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TRANSACTIONS

OF THE

CONGRESS

OF

American Physicians and Surgeons

FIFTEENTH SESSION

HELD AT

WASHINGTON, D. C.

May 9th and 10th, 1933

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TABLE OF CONTENTS

Table of Contents iii

Titles of Papers to be read at Congress iii

Officers of the Congress v

Executive Committee vi

Committee of Arrangements vii

Past Officers of the Congress viii

By-Laws of the Congress ix

Minutes of the Fifteenth Session of the Congress x

Guests of the Congress xi

Visitors lxxi

Recapitulation lxxiv

THE PRESIDENT'S ADDRESS:—MEDICINE AT THE CROSS-ROADS; BY DR. HARVEY CUSHING 1–24

THE FEMALE SEX HORMONES 25–76

The Present Position of Our Knowledge of Anterior Pituitary Function; by Dr. Herbert M. Evans 25–46

Studies on Anterior Pituitary Physiology; by Dr. J. B. Collip 47–64

The Application of Endocrinology to Gynecological Problems; by Dr. Emil Novak 65–76

Discussion:

Dr. Carl G. Hartman 77–79

Dr. Robert T. Frank 79–80

Dr. Henry Alsop Riley 81–85

PRESENTATION OF KEYES MEDAL 86–90

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1933—Dr. Francis R. Hagner, Washington, D.C.

BY-LAWS OF THE CONGRESS

OF

AMERICAN PHYSICIANS AND SURGEONS

1.

This organization shall be known as the

CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.

2.

It shall be composed of national associations for the promotion of medical and allied sciences.

3.

It shall hold its sessions at 5 year intervals in the city of Washington, D.C.

4.

The officers of the Congress shall be a PRESIDENT, VICE-PRESIDENTS, A SECRETARY, A TREASURER, AND AN EXECUTIVE COMMITTEE.

5.

The PRESIDENT shall be elected by the Executive Committee, of which he shall be *ex-officio* a member. He shall preside at the sessions of the Congress. He shall deliver an address.

6.

The PRESIDENTS of the participating societies shall be *ex-officio* the VICE-PRESIDENTS of the Congress.

7.

The SECRETARY and the TREASURER shall be elected by the Executive Committee. They shall be *ex-officio* members of the Executive Committee.

8.

The EXECUTIVE COMMITTEE shall be composed of one (1) member from each participating Society and said members shall be elected by the various Societies at the next annual meeting subsequent to the Congress.

It shall be charged with all duties pertaining to the organization of and preparation for the ensuing Congress, including the election of all officers and of a Committee of Arrangements.

9.

The expenses of the Congress shall be divided between the participating Societies in proportion to their membership.

10.

The admission of new associations to participate in the Congress shall be by unanimous vote of the EXECUTIVE COMMITTEE.

MINUTES

The fifteenth session of the Congress of American Physicians and Surgeons was held in the Auditorium of the National Museum Washington, D.C., on May 9th and 10th, 1933.

The first session was called to order at 8 P.M. Tuesday, May 9th, by the First Vice-President, Dr. Oscar M. Schloss of New York City, President of the American Pediatric Society. Dr. Schloss introduced the President of the Congress, Dr. Harvey Cushing, who spoke on the subject "Medicine at the Cross-Roads." The Congress was then adjourned to an upper floor where a reception to the President was held, and a buffet supper served.

On the afternoon of Wednesday, May 10th, the general scientific session was held at 2:30. The President presided and introduced the various speakers who contributed to a symposium on "The Female Sex Hormones." Addresses were made on this subject as follows: By Dr. Herbert M. Evans (by invitation), of the Rockefeller Institute for Medical Research, New York City, on "The Present Position of our Knowledge of Anterior Pituitary Function"; Dr. J. B. Collip of McGill University, Montreal, on "Studies on Anterior Pituitary Physiology"; and Dr. Emil Novak of the School of Medicine, Johns Hopkins University, Baltimore, on "The Application of Endocrinology to Gynecological Problems." Discussion of these papers followed by Dr. Robert T. Frank of New York City, Dr. Henry Alsop Riley of New York City, and (by invitation) Dr. Carl G. Hartman of Baltimore.

Following the symposium the Keyes Medal was presented by the American Society of Genito-Urinary Surgeons through its spokesman, Dr. Wm. C. Quinby, to Dr. Alfred Newton Richards.

The meeting was then adjourned.

CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS

Report of Treasurer, October 1, 1933

RECEIPTS

Cash Balance from previous Treasurer	$1,830.35	
Balance from Dr. Shands after paying expenses of Chairman	785.00	
Registrations received by Treasurer	1,780.90	
Total Receipts		$4,396.25

DISBURSEMENTS

Printing (envelopes)	$ 22.50	
Printing (notices)	152.50	
Advanced to Dr. Shands (postage, etc.)	50.00	
Postage for Treasurer	12.00	
Loss by exchange on Canadian checks	7.23	
Printing (registration blanks)	59.75	
Rubber stamp	.70	
Printing (placards)	39.50	
Printing (programs)	392.82	
Orchestra (reception)	65.00	
Refund of registration fee	5.00	
Refreshments (reception)	600.00	
Attendants at reception	97.00	
Floral decorations (reception)	15.00	
Miscellaneous expenses, Dr. John T. King	48.02	
Miscellaneous expenses, Dr. Carl G. Hartman	2.50	
Miscellaneous expenses, Dr. F. R. Hagner	5.00	
M. L. Powderly (Clerical work for Dr. Hagner)	75.00	
Reporter at Congress (Mrs. Alvares)	58.60	
Tax on bank checks	.38	
Total Disbursements	$1,708.50	
Balance on hand—on deposit in checking account, American Security and Trust Co., Washington, D. C.	2,687.75	
		$4,396.25
Estimated cost of publication of Proceedings of Congress	$ 787.00	
Estimated balance after payment for publication of Proceedings of Congress	1,900.75	

Francis R. Hagner, *Treasurer*
Congress of American Physicians and Surgeons.

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By Invitation of the Executive Committee

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Founded 1864

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Dr. Abraham E. Jaffin,	Jersey City, N.J.
Dr. Franklin Jelsma,	Louisville, Ky.
Dr. Robert W. Keeton,	Chicago, Ill.
Dr. Edward A. Knowlton,	Holyoke, Mass.
Dr. Lewis Henry Koplik,	New York City.
Dr. John G. Kuhns,	Boston, Mass.
Dr. Grant H. Laing,	Chicago, Ill.
Dr. G. Paul La Roque,	Richmond, Va.
Dr. Jean Macnamara,	Melbourne, Australia.
Dr. John Willis Macy,	Rochester, Minn.
Dr. Charles C. Marbury,	Washington, D.C.
Dr. T. C. Moss,	Memphis, Tenn.
Dr. R. J. P. McCulloch,	Toronto, Canada.
Dr. Laucklen McPherson,	East Saint John, N.B., Canada.
Dr. Jost Michelsen,	Leipzig, Germany.

Dr. Henry Milch,	New York City.
Dr. John Walker Moore,	Louisville, Ky.
Dr. S. B. Muncaster,	Washington, D.C.
Dr. C. J. Noonan,	Brooklyn, N.Y.
Dr. George C. Prather,	Boston, Mass.
Dr. W. P. Reeves,	Washington, D.C.
Dr. Albert W. Rounds,	Providence, R.I.
Dr. S. W. Sappington,	Bryn Mawr, Pa.
Dr. Constance Schradieck,	Providence, R.I.
Dr. Francis A. Scott,	Huntington, W.Va.
Dr. Murray Sempson,	London, Ont., Canada.
Dr. Geo. F. Skinner,	St. John, N.B., Canada.
Dr. Walter Fox Smith,	Watertown, N.Y.
Dr. Carl R. Steinke,	Akron, Ohio.
Dr. John L. Stifel,	Toledo, Ohio.
Dr. Welland C. Stoner,	Cleveland, Ohio.
Dr. W. W. Stoner,	Tuckahoe, N.Y.
Dr. Gregory Stragnell,	New York City.
Dr. L. E. Stubbs,	Newport News, Va.
Dr. Virginia Tannenbaum,	Buffalo, N.Y.
Dr. Erik Atk. Upmark,	Boston, Mass.
Dr. Earl E. VanDerwerker,	New York City.
Dr. P. J. Vivier,	New York City.
Dr. Thomas Wheeldon,	Richmond, Va.
Dr. Elihu S. Wing,	Providence, R.I.
Dr. Russell S. Wolfe,	Elkins, W.Va.
Dr. Samuel H. Zia,	Boston, Mass.

RECAPITULATION

	Emeritus, Senior, Active and Associate	Corresponding	Honorary	Present
American Ophthalmological Society..	186	..	..	42
American Otological Society.....	150	..	8	16
American Neurological Society.....	192	..	29	36
American Gynecological Society.....	94	..	34	17
American Laryngological Association.	121	20	2	15
American Surgical Association.....	223	..	20	66
American Climatological and Clinical Association.....	194	8	16	75
Association of American Physicians..	280	2	16	115
American Association of Genito-Urinary Surgeons.....	79	12	6	27
American Orthopedic Association....	150	11	8	37
American Pediatric Society.....	119	2	13	35
American Association of Pathologists and Bacteriologists.....	465	..	..	69
American Association for Thoracic Surgery.....	141	..	5	39
	2394	55	157	589
Total Membership of Congress.....		2606		
Guests and Visitors.....				85
Total attendance.....				674

THE PRESIDENT'S ADDRESS

CONGRESS OF PHYSICIANS AND SURGEONS

INTRODUCTORY REMARKS

Dr. Oscar M. Schloss: It has been the custom according to the By-Laws of the Congress of American Physicians and Surgeons that the President of the Congress be introduced at the time of his address by one of the Presidents of the constituent organizations. It now devolves upon me to introduce one whom many of you know personally and whom all of you know by his work and reputation. I, therefore, present to you Dr. Harvey Cushing who will address you on the subject of Cross-Roads in Medicine.

MEDICINE AT THE CROSS-ROADS

HARVEY CUSHING, M.D.
Boston, Mass.

In April of 1918, a Canadian Casualty Clearing Station had been newly set up, in the emergency of that critical time, at a hamlet called Pernes somewhere near Bethune in Flanders. The surgical "teams" as they were called, hurriedly assembled from where they could be spared, were working on day and night shifts like factory hands to keep abreast of the raw material fed in to them. We dealt with wounds—not the man. For him we had no time. Some far away government took that responsibility, and is still paying for it. In the midst of this, on an afternoon while in the course of one more gruesome task, I was suddenly told by a much annoyed Commanding Officer that orders had been received from the A.E.F. for me to report forthwith at a place called Langres.

Anything may happen in time of war, and one asks not why. Langres, as it turned out, was a perfectly safe hill-town half way

across France between the headwaters of the Marne and the Meuse. And not knowing whether I was to be demoted for some breach of discipline or made Commander-in-Chief, with ill-concealed agitation I presented myself there in due course before the C.O. of what proved to be a training school for Army medical officers. I was informed I had arrived just in time to give the noon lecture on battle injuries of the head.

Of that impromptu and futile lecture—after which I was dismissed—the less said the better. I was picked up by a sympathetic friend permanently attached in Langres—a first Lieutenant, considerably my senior in years, who in normal times was a professorial colleague. He offered to take me to lunch at his mess before my departure. On the way there—and I at last approach the point of this recital—we passed, in a narrow street, the open window of a shop in which, concentrated on his work, there sat before a bench an oldish man in shirt sleeves and a leather apron making jack-knives. He wasn't making parts of knives, but the whole knife—steel blades, bone handle, and all; and some of them, finished, were hanging in the window alongside a much faded blue tunic with a wound stripe on the sleeve, which told its own story.

Were his knives for sale? Yes; since times were hard, only six francs for the better ones, and we could step in and have a look if we desired. A pocket knife may sometimes be useful to cut red tape, and when I had made a selection he examined the knife carefully, put it back and took another which he said was a better one. If I didn't lose it, it would last all my days; and would I notice the spring—no breaking of fingernails with a carefully made and tested knife like this—a masterpiece if he said so as shouldn't. So admiring was he of his handiwork I began to think he would not bring himself to part with it; but his decision to do so was suddenly stiffened by the entry from a back dwelling-room of his wife and two children—future jack-knife makers in all probability.

Not long after this, I somehow or other happened to sit in at an informal discussion between two French officers and two American efficiency experts, members of an advisory commission that had been sent to France. Plainly the reason the Allies had not already won the War was their want of industrial organization, their inability, for lack of proper machinery and modern methods, to turn their raw materials rapidly enough into the finished product and to give it wide distribution. The only way to do this ef-

fectively was the way we made motor cars in America, each workman contributing his small part, at high speed, in short hours, for good wages.

After much more in similar vein, the senior French officer finally said: "This may all be true, gentlemen, but it would be almost better for us to lose the War. The French artisan works because he likes to, often at his home, can turn his hand to many things, is frugal and content with small earnings, can usually make, pretty much with his own tools and hands, some finished product which he can sell. So even in trying times like these, he gets independently to work as his own employer, somehow supports himself, and merely asks to be left alone. Were he forced into being a piece-work specialist he would lose his resourcefulness and independence of action. Should this happen on a large scale, discontent would surely follow and our social order fall to the ground."

That night I fell asleep thinking of the Langres knife-maker. Every foot-soldier should have a jack-knife—not just an occasional officer. There must be a more even distribution of bigger and better and sharper knives. All independent knife-makers in the emergency are congregated in a factory where some do the blades, some the handles, some the assembling of parts, the labeling and packing, the advertising, the selling, the foreign distribution—everyone a specialist in his own line. It becomes a great business, a marvel of efficiency. Jack-knives are quoted on the stock market and prices soar. New machinery is installed whereby synthetic knives can be turned out by the million almost without aid of human hand—and everyone knows the awakening. A glut on the market, a closed factory, all knife-makers out of work; and even those few who still remember how to fashion a good, complete jack-knife from the raw materials no longer able to sell them, join the others, march on Paris behind the red flag of protest, and demand from the government either a dole or a new sorting of the cards. Whereupon a group of well intentioned philanthropists, sociologists, economists and lawyers, together with two former knife-makers, one now a specialist in corkscrews, the other in synthetic-bone handles, are appointed to study in all its aspects the relation of knife-making to the common weal.

This, after all, is not much of a story—partly a dream at that—and perhaps only by a stretch has it anything to do with the present crux in which the medical profession finds itself, over-manned,

over-specialized (behold this Congress!), like other necessities of life poorly distributed, an expensive luxury for those of modest means and the subject of investigation by a commission which threatens us with socialization unless we promptly do something to alter our spots, to cast off our long-conditioned reflexes, and put ourselves on a modern chain-store business basis. This for the next twenty-five years at least, and that's as far ahead as there is need to plan, will serve to make everyone—including the doctor—happy, healthy and wise.

A lawyer on the Commission goes so far as to use the ugly word "coercion" and when a friend, familiar with jurisprudence, was asked just what that meant, he said "Government by force." And to the question whether it would be possible similarly to "coerce" the legal profession into caring for persons of modest means on the same parity as the well-to-do, he replied: "No, the lawyers are too smart, and there is too large a percentage of them in our legislative bodies ever to bring such a thing about."

A recent leader of public opinion openly states that most of those at present dealing with the sick—meaning more specifically the doctor—have their faces turned toward the past. If history but repeats itself, where else but from the past *can* we learn anything? We certainly can draw little comfort and few admirable lessons from the late present. Nor would this seem to be the time to fly to evils we know not of, but rather to stick firmly to what has proved in the long run the great stabilizer—every honest man with faith, hope and a stout heart going about his own business, with swift punishment for dishonesty and crime. And lest we forget, let us for a moment in reality *turn* our faces to the past:

> The prevalence of crime he assigned to want of employment among the poor, to the idleness and the luxury of the well-to-do, to the recklessness with which the rulers engaged in war. Discharged soldiers, troops of dismissed retainers from the households of the gentry, who, after a life of idleness, were thrown on their own resources, ploughmen and peasants, whose services were no longer required by the sheep-farmers, perilously swelled the ranks of the unemployed and made thieving the only means of livelihood for thousands of the population. A more even distribution of wealth was essential to the country's salvation. To this end were necessary the enjoyment of the blessings of peace, restrictions on the cupidity of the capitalist, improved education of the humbler classes, and the encouragement of new industries.

While this might have been written of many times and places

since then, it in effect was what the old sailor, Raphael Hythloday, had to say concerning the status of England in the sixteenth century. Things were quite different, he said, on the isle of Utopia whence he had recently returned. There everyone lived in complete social happiness and brotherly love; disdaining money, they wanted for nothing, not even hospital care, and could worship as they chose.

Needless to say, when the crisis came in his own affairs, the author of this more often quoted than read allegory, with the inconsistency that affects mankind, failed to live up to his expressed ideals, attempted to coerce others to his own theological beliefs, and lost his head in the process. Social reformers, no less well intentioned and lovable characters than was Sir Thomas More, sometimes lose their heads though not always in just that way. More's great friend, Erasmus, wrote a famous skit in praise of folly; and More doubtless knew well enough that "the greatest folly of which a man is capable is to sit down with slate and pencil to plan out a new social world," though we waited almost four hundred years for a student of society to say just that.

Heaven knows there are plenty of things the commoner, including most doctors, would like to see corrected and the sooner the better—dishonesty among those entrusted with other people's savings, less interest in legal procedure and more justice among the lawyers, as examples—and the doctors wonder why, just at this time, when in spite of widespread distress and anxiety the health of the people as a whole is better than ever, he should be particularly singled out and told if he doesn't distribute himself more evenly, stop specializing and charge less, he'll be coerced into doing so.

He thinks this highly peculiar, for hasn't he always striven with ever increasing success to eliminate one after another the diseases whose particular care provides his bread and butter? And has he not shared with the priest, from the beginning of the record, in giving a large part of his time to the indigent poor in whom business, finance, and the law may be theoretically interested without showing it in so direct and practical a way?

Lay reformers speak lightly of his code of ethics as something long since outworn, but so far it has prevented him for one thing from capitalizing for his own benefit his inventions and therapeutic discoveries. If Jenner and Lister had been trained in the

point of view of modern business efficiency, instead of being just a plain, improvident country doctor and a young hospital surgeon, whose only desire was to help others and to stand well in the esteem of their professional fellows, what then? For the discovery of the practical application of ether anaesthesia, Medicine has no corresponding hero because someone, having unethically taken out a patent, proposed to sell it to the government for a large sum and very nearly succeeded in doing so—all of which is thoroughly ventilated in five hundred and eighty-two printed pages of testimony before a select committee of the United States Senate to their great waste of time. For what could be their understanding of an ancient profession's precepts in regard to what its votaries may and may not properly do?

It is preposterous, writes the efficiency expert, to say that a man even a doctor, is not entitled to what he can make out of his inventions. The medical man of the future will pay more attention to prevention than to cure, says the young D.P.H. to his hostess as he accepts his second cocktail. The social reformer, stopping at the corner store for his favourite brand of cigarettes, purchases a sixty-cent bottle of the latest "pectoral" which the clerk says will be good for his (easily preventable) chronic cough; and, dear me, he's almost forgotten his promise to fetch home Aunt Maria's weekly bottle of Lydia E.'s Restorer at $1.25—for though it isn't so restoring as when it contained forty percent, she still takes it after meals.

Knowing their frailties, the doctor doesn't think over much of his fellowkind while doing what he can to prevent, alleviate or cure their ills. He at least doesn't overrate them and treats like anyone else the chiropractor, and the science healer (secretly), and the veteran who draws a total disability allowance yet is on the police force, and even the prosperous-looking uplifter of society, knowing that each of them will look surprised when asked to pay for his services and that so far as concerns *them*, he'll soon join the ranks of others never thought of.

It is not with such as these that the doctor shows his best side. He feels far more at home with the ordinary, self-respecting people of modest means who don't expect, on this earth, to find green pastures provided for them, with ten-cent cigars, a two-car garage, and a fish-fry in every dinner pail. They frankly say just what their circumstances are and what they can pay and when. For them, too,

he can do no more than his best and only wishes it could be better, and cuts their bill in half or cancels it altogether. They never forget him but send him each year a note on the anniversary of the operation and, like enough, a pair of carpet slippers for Christmas which he can't use for he's in his boots till bed time. But this he doesn't admit when making his acknowledgement, for he cherishes their remembrance—even their gratitude though pretending not to like it. And as a matter of experience, those who can least afford it are the ones among his patients most eager to make a prompt cash payment to him, even though a large part of every hard-earned dollar goes to various unseen persons whom they are making rich, and to whom they feel obligated in no comparable way.

In his commonsense discussion of the ever shifting manners, mores and morals of society William Graham Sumner had much to say to the undergraduates at Yale a generation ago about a particular man who is never thought of and on whom the burden always falls. In the complexity and rivalry of human interests, he is the one who in the end always has to pay—even for the efforts of social reformers to make the world over.

In the issue before us, if I may venture to paraphrase Sumner, everyone's sympathy, including that of the reformer *A* and his friend *B* who stands financially behind him, lies with the self-respecting person *X* of modest income, who finds it difficult, to meet the expense of medical care in case of sudden illness or accident from some unpredictable and unpreventable cause. For the sake of *X*, this particular evil must be remedied by a statute which will determine, not what *A* and *B* *might* do for *X* themselves, for they would need no legislation for that, but what an intermediary —in this case the doctor—*C* *must* do for him.

Now *X*, who has not been consulted, will be likely to say when he gets wind of it, that after all, he doubts whether he will ever need doctor *C*, even should he prefer him, when the time comes, to another medical man of his acquaintance. What is more, he is already burdened with more insurance and taxes than he can afford. He is already paying to support the local, state and an expanding federal board of health, for prisons to accommodate the rapidly increasing number of criminals, for institutions to house the even more rapidly increasing insane and feeble-minded, for hospitals to care for that organized group calling themselves "veterans" who

may not increase in number, but do in their demands, which amounts to the same thing.

So he and his neighbors conclude, in accordance with Sumner's social philosophy, that in this instance they as usual will again foot the bills, just as their common kind originally paid, little by little, all that now fills the coffers of *A*'s philanthropic friend *B* of the Foundation which is backing the proposal. And from all he can gather, so far as the public purse is concerned, the old adage which likens it to holy water still holds true—those who have access to it help themselves.

Unfortunately, *X* is not always so sensible a fellow as to make a family friend, confidant and adviser of one or the other rival practitioners in his small town. And when the *X*'s gravitate to the city, and shift from place to place when there, you and I know they are more apt to choose an abode convenient to a cinema and a drugstore than a doctor. When a member of the family takes ill and fails to respond to the usual proprietary remedy, a neighbor is consulted who turns out to be a Christian Scientist; or another who suggests the particular chiropractor who for five dollars cured Uncle John of the flu at one sitting; or a third who has just seen in the morning paper the name of a perfectly swell professor who has just done something wonderful at the New Medical Centre to a woman who swallowed her false teeth.

Acting on this suggestion, he is called on the telephone and asked if he won't please come immediately to No. so-and-so in Harlem to see a sick woman just in his line of work. No, they have no family doctor; so he asks if there is not a doctor in the neighborhood they can more conveniently and promptly call in. "Yes, there is a Dr. Jones just around the corner but we don't know him as we've only lived here nine months and never needed a doctor before, and anyhow he is only a house-to-house doctor, and the case is so urgent we need a specialist at once and we can't afford to go to the hospital, it's so expensive."

Our urban populations are largely composed of people of just this sort, and what's to be done to save them against themselves and keep them from "shopping around" as it's called? Ten chances to one there is nothing seriously wrong with this panicky woman, and the chances are also ten to one that the local doctor will prove capable and efficient, will promptly grasp the situation, know how to deal with it, and gain the confidence of the family and their

friends. "Such a nice doctor, so scientific; and to think we've never known about him before! Why, he cured Mother's trouble in one visit and only charged two dollars though he's a great friend of the professor at the Medical Centre whose name was in the paper." But who is this house-to-house doctor so suddenly sprung upon us? He has supposedly gone out of business, pinched on one side by the public health officer and periodic life-extension examiners, and on the other side by what are called the scientific doctors, including ourselves, the specialists in our respective hospitals. He has long been so far forgotten he should by this time be an extinct species. Indeed, it is authoritatively said that the automobile and the associated highways together with the present "set-up" of society have driven out the unmethodical, silk-hatted, bewhiskered lovable and friendly general practitioner.

This scornful picture of the practising doctor shows lack of knowledge, besides being somewhat cruel. Whiskers and a silk hat don't make the man. Fashion makes the whiskers; and the boys in blue were as good soldiers for all their beards and Bull Durham as were those in khaki with their clean faces and fags—too many at that. Gillette and Henry Ford and the Dukes may through advertising and salesmanship change our appearance, our manner of getting about, and incite us to bad habits—incidentally with great profit to themselves. But even though his whiskers have gone with his tall hat, if he ever had one, and he comes in a cheap motor car instead of behind a horse, and nervously smokes too many cigarettes, the general practitioner or family doctor is still with us, and plays the same important rôle he always has.

For nine-tenths of what he is called upon to do "the operating table and the microscope and the Roentgen Ray and the trained nurse and the mechanotherapeutist" are wholly *un*necessary; and when they are needed he usually knows where to get at them. All he asks from his school is that, under teachers who know from experience rather than theory what his life work is to be, he may get the sort of well rounded training which will enable him to keep abreast of the changing times while in the city or country, with dignity and propriety, he engages in the quiet art of healing.

Such are the men who represent the backbone of our profession and for each of them there are countless devoted patients and for each patient whole families whose voice in our discussions has not as yet been heard. And were it heard, it would be, in effect,

what it always has been: "So long as I am well, I forget the doctor —and his bills which he often neglects to render; but he is always there in case of need except during a vacation, something I notice he is more apt to prescribe for others than take himself."

It is to the self-sacrificing spirit of the sagacious practising doctor, not to the likes of us in this, that or the other line of special work, or the medical scientist, or the public health official that from the earliest times tribute has been paid.

> Honour the physician because of the need thou hast of him; for the most High hath created him . . . and in the sight of great men he shall be praised. All healing is from God. He hath created medicines out of the earth, whose virtue is come to the knowledge of men who shall thereby cure and allay pain.

So, in effect, in the Book of Wisdom did the son of Sirach called Ecclesiasticus admonish the average man and potential patient, who differs no whit to-day from some nineteen centuries ago. He is no less gullible and superstitious, no less negligent and sinful, no less certain from time to time to betake himself to a physician, from whom he expects, and usually gets, not only understanding and sympathy but an honest opinion—accompanied by emphatic directions which it is to be hoped he will follow longer than he does his own good resolutions made each New Year's eve.

A remark, easily traceable to its source, has been often repeated to the effect that the family doctor will come to be replaced and crowded out by the local health officer. Preventive measures against the spread of disease are no new thing. The very word quarantine and its mystic forty days and forty nights is lost in the darkness of oriental history long before Hygeia, the daughter of Asclapius, was worshiped as a health-protecting divinity. Even today when we are said to be more "scientific," our legal enactments relating to the public health still apply chiefly to the transmissible diseases; and the doctor has had much to do with bringing about the sanitary well-being of the community by hammering into the ears of reluctant legislators the necessity of permanent, non-political, state-paid officers whose enlarging powers become increasingly international in scope. What the doctor asks and expects of them is that the hard won ground he has gained be held and consolidated, so he can quietly go about his preparations to gain more, by pushing out another salient when all is ready for a concerted attack.

By the combined efforts of both groups, doctor and sanitary official, the expectancy of life has been greatly prolonged—and will be more so before we are through. Yet while we point to this triumph, there are just so many more people who live longer only to be overtaken, the health official with the rest, by unforeseen and unpreventable accidents for which they seek the best surgeon they can find, or by some malady for which they demand the very best physician—like enough a highly trained specialist.

In short, for every disease from the beginning of time we have learned to escape by prevention, or to alleviate and even cure by drugs, there remain disorders beyond enumeration we cannot yet dodge because we don't know their cause. And even when this slowly and laboriously is determined for one malady after another, so that it may in turn be eliminated, would people only obey the laws of health, something else promptly crops up to take its place, for hitherto unsuspected derangements of our poor bodies are being detected and described almost daily.

Three-fifths of the practice of medicine depends on common sense, a knowledge of people and of human reactions. More than half of the remainder is technological and mechanical, the work of those medically trained artisans we call surgeons. What remains may be termed preventive; and this in bulk very properly and inevitably comes to be taken over by the state, though people, being what they are, find ways of evading a disagreeable statute as in the case of compulsory vaccination—intended for others but not themselves. Not everyone obeys the traffic light and every regulation breeds its jay-walkers and its racketeers.

Legislation and attempted coercion do not always accomplish what reformers anticipate. The country's recent quixotic experience with prohibition, the most important health measure ever sanctioned by a government, however well intentioned, probably set back rather than quickened that much to be desired goal of national temperance which by natural processes was slowly gaining ground. At great expense, a commission sat long and wearily on this subject, again without coming to a unanimous voice. And finally the mass of sober, obscure people of small means, who as usual were bearing the chief expense of enforcing a law which was breeding crime and disobedience, though inarticulate, at least could vote. So almost as one they decided, in spite of the lost ground and its disheartening confusion, to take a fresh start toward the slow

cultivation of national restraint in the use of intoxicants. "The fallacy," said Sumner, "of all prohibitionary, sumptuary and moral legislation to protect people against themselves is the same."

There has been much idle talk, too, regarding scientific medicine and the modern scientific doctor who with his ingenious appliances and mathematical exactitude has come to supplant the oldfashioned "practical" doctor. For hasn't he—or mostly his trained technicians—taken our blood-pressure, our electrocardiograms, our basal metabolic rate, lumbar punctured us, ophthalmoscoped us, ventriculogramed us, x-rayed us from top to toe, studied under the microscope everything we can expel for him besides drawing off our blood for the same purpose, looked in all our orifices, tickled the soles of our feet, charted our calories, our calcium and phosphorus and nitrogen intake and output? It's peculiar after all that time and expense they can't seem to tell why Johnny has fits; perhaps blunt old Dr. Brown up country was right when he said that Johnny, during that attack of flu, had what *he* would call inflammation of the brain and the city doctors encephalitis lethargica—for which they charged more. But whatever it was called, he was sorry to say it couldn't have been prevented, nor was there much he or anyone else could do for it, and we'd just have to grin and bear it.

As a matter of fact, it will be a great shock to laymen to learn that a great part of what is called scientific medicine is a fetish and wholly *un*scientific. We have instruments of precision in increasing numbers with which we and our hospital assistants at untold expense make tests and take observations, the vast majority of which are but supplementary to, and as *nothing* compared with, the careful study of the patient by a keen observer using his eyes and ears and fingers and a few simple aids. The practice of medicine is an Art and can never approach being a science even though it may adopt and use for its purposes certain instruments originally designed in the process of scientific research. In the case of Mary who got behind at school it's been found, to be sure, that her basal metabolic rate was minus five per cent, so she is now taking thyroid extract, and though it makes her nervous it's scientifically correct, the doctor says, and she must keep on with it. In spite of all the discouraging things they are permitted to learn about the units composing society, the doctor and the priest continue to have not only hope for but faith in their fellow men and

expect them, in spite of their frailties, to be unselfish and honest till they prove themselves otherwise; whereas in trade, politics and the law, we are told, a man is primarily taken to be self-seeking until he proves the contrary. It may amount to the same thing in the end, but it at least shows a different approach; and it may partly explain why the doctor, compared with others, is known to be a poor business man. This, after all, may not be an unadmirable trait even though the dollar is taken to be the common measure of "success" in our present-day world which looks scornfully on his financial incompetence.

I recall once being at 13 Norham Gardens in Oxford when the Regius Professor received a cable from a Maharaja in India: "Request you see son injured yesterday's polo game. God will pay the bills." The Regius promptly acted on this request, cabled reassurances to the Maharaja, and charged it up to the Almighty, already heavily in his debt. No, the doctor in the past has not been good at business and most of those who happen to possess that talent soon leave the profession for fields where they more properly belong.

Why he should refrain from forcible collection of his unpaid bills; why he does not patent some of his prescriptions, inventions and discoveries and make a fortune; why he should continue to counteract the spread of diseases he has painfully and at great educational expense learned how to diagnose and treat; why he should so strenuously oppose year after year the efforts of anti-vivisectionists and anti-vaccinationists with their Christian Science allies to cripple research and to annul statutes already on the books, knowing his calls would increase did they have their way; and why at the same time he should continue to work for longer hours for less pay during a shorter life of activity than most people is an enigma to a hardheaded business man.

To be sure, business is now recognized as one of the professions in certain educational circles, but whether this will elevate the ethics of business which is fundamentally competitive rather than fraternal, or whether it will undermine the code of Medicine remains to be seen. With business goes advertising, and there are few forms of it more profitable than the manufacture and sale of proprietary medicines over the same counter with candy, cosmetics and cigarettes. Even science has unblushingly begun to spread her experimental discoveries in the raw before the public

by fostering a lay journal for the purpose. And since everyone is doing it, how long will the doctors continue as a class to resist? When they no longer do, and adopt the advertising methods of those parasites of the profession, the quack and the patent mediciner, God help the man of modest means and everyone else, whether below him or above him in the social scale, who may some day need a doctor.

He, the man of modest means, is at the mercy of an organized racket beside which "bootlegging" was as child's play, for that was a nocturnal game and this is played in the open. Lost somewhere in the Department of Agriculture is a Food and Drug Bureau which does its feeble best to control what is printed on the package advertisements. But only the Federal Trade Commission, which probably is composed of lawyers, could, if they saw fit, put a stop to the falsehoods the press continues to carry regarding the contents of the package. And when such a thing as an influenza epidemic comes along and every newspaper in the country is spread with advertisements of cheap proprietary sure-cures, what are the people to believe? If any embarrassing questions are asked, you may be certain that your congressman has already been instructed by a well organized lobby not to interfere with what is a profitable business.

The explanation of the doctor's seeming want of business acumen lies partly in the restraining influence of his time-honored precepts of conduct, partly in his preference to hold the respect of his own kind rather than of the financial world, and partly because inherently he's that kind of person else he wouldn't have gone into Medicine in the first place. He's already done a great deal not only for the poor but for the man of modest means as well, and it is offensive to be told by a board of lay people that he's neglecting them.

I have been led to look up the records of my one hundred and fourteen medical classmates who after a three-year course were turned loose on the community now almost forty years ago. Some sixty percent of them went promptly into general practice, and too many have broken down or died ahead of their patients. And though the survivors are modest fellows who don't like to talk even to a schoolmate about their measure of sucess, far less of any grudges they have against the world, what they do say runs something like this: "I'm in general practice in the small town where

I was born, and proud of it. I've been sufficiently successful to raise and educate a family. I've served my country as a first lieutenant in time of war, and for a longer time my district as health commissioner in times of peace. I still retain my self-respect—with the exception of giving out liquor prescriptions. *Distinctions:* none, not even having a baby named after me, which is unusual for a country doctor. *Hobby:* my family, my patients, and a keen interest in world events."

Now to what I would chiefly call attention is that, of these graduates of forty years ago, who have lived in town or country the lives of general practitioners, a large percentage of them have served their communities in some public capacity, more often as health officer or as member of the local health board. But a basic medical education is no longer considered either desirable or necessary for the holders of such positions. The health officer must be a specialist among other specialists with which Medicine is already overloaded.

Stirred by what may be accomplished in checking the spread of certain bacterial and protozoal diseases by a medically trained Gorgas or a Leonard Wood, in the hope of perpetuating their species, a vast sum of money is set aside to educate separately and by a short cut those who are to take their places, all too often political appointees, which means for all of us a little higher tax. But when it comes to the ever recurring fight against adverse legislation relating to tuberculous cattle, to compulsory vaccination, and much else, it's again the doctor, personally known in the legislator's home and with no conceivable axe to grind, who must usually come to the defence of the paid local official lest ground be lost.

I don't for a moment mean to imply that we should go back, for there's no going back. I merely wish in fairness to recall what the practitioner in the past has done to safeguard public health and to point out that the chief burden of expense, when government enters in, always falls most heavily on the same man of modest means. And could he be heard, he would probably say: "Go slow with this proposal to insure me against those innumerable ills beyond the control of the health officer. It will mean an elaborate organization of persons to make the system work; some form of racket will certainly grow out of it, far worse than the veteran racket; and even should the state take it over, it comes out of my pocket just the same."

And if the average man feels uneasy over the obligation to carry some additional insurance, the doctor feels even more so from his experience, at close hand, with the system of employer's liability insurance, now compulsory in certain states, and which is a veritable hothouse of malingering. The impractical doctor at this juncture, after reading the reports of the Commission, ventures, half aloud, to suggest that the most effective and least burdensome form of voluntary health insurance would be for everyone to cut in half his (or her) annual expenditure for tobacco, which would not only leave more than enough in the family budget to pay all the costs of medical care in the family but would eliminate a multitude of incapacitating nervous disorders in the bargain. To this the Economist scornfully replies that such a mad scheme would be ruinous to the tobacco planter, would undermine the huge superstructure of industry that he carries, would put an end to the alluring illustrations of smoking females which beautify the magazines and the countryside, and though there is not a cough in a carload, one mustn't forget that the U. S. Treasury gets six cents on every package sold.

Alongside of this agitation regarding the expense of doctoring has gone a careful study of the prevailing trend of medical education. And as many of us here have been, or are still, actively engaged in teaching, we have all probably asked ourselves—even ventured to ask in faculty meetings—just what are we trying to make of our medical students? Departments multiply and every teacher, if he's what he should be, believes his own field to be of major importance; and there lurks in his breast the hope that some few of the leaders in each class before him may be lured into his special subject.

From the first day, therefore, the prevailing system points toward that very thing which we now decry—over-specialization. And since science is now everywhere in the saddle and chief emphasis is laid upon it, the premedical sciences have first say and we tend more and more to carry great institutions of research as appendages to our schools now manned in increasing numbers by teachers who have had no medical training, far less actual experience with the handling of patients.

I don't mean to say that this is all wrong and that there should be a bouleversement; I merely wish to point out that it makes the training of the doctor a long and highly expensive process and has

had not a little to do with the expense of medical treatment. In actual fact, our schools no longer pretend that the degree of M.D. which students attain after four years prepares them for practice; we merely bring them to the point at which they must on their own initiative scramble for a hospital appointment where they hope to acquire what the school has neglected to give them—the training necessary to secure a license to practise.

With the degree the school's responsibility—even interest—appears to end; and no school that I know of makes a consecutive and comparative study of its educational product. The surgeon in these later days who does not conscientiously follow up his cases to know what may be the ultimate outcome of the operations he performs is looked upon as an undependable routinist, and one would suppose that every medical school would wish to know what was the end-result of its teaching. In my own school, at least, there is no such record beyond what is kept for social purposes by class secretaries, so it is impossible to learn, apart from the meagre information supplied by the national directory of physicians, how many men to-day compared with forty years ago are attracted into the sciences, immediately take up a specialty, turn to some salaried position in public health or one of the services, or largely go as of old into general practice.*

There has been much lamentation about the disappearance of the family doctor but as already shown, he's not often heard from and I am far from believing that he's a vanishing species, in spite of our scholastic neglect of him in a system, which by over-emphasis on research and prevention, rather than on diagnosis and treatment, gives him while an undergraduate a sense of inferiority which he hopes to overcome by going quickly into a small special field of surgery or medicine, however ill prepared.

And should the report of the Lowell Committee lead our Class

* It is quite possible that the tendency toward specialization has been considerably overdrawn. Just because a practitioner limits himself largely to internal medicine, to surgery or to obstetrics does not justify classifying him as a specialist. Every general practitioner comes to be known in his community and recognized by his fellows as possessing unusual skill, due to experience and good luck, in a certain type of cases. Hence, he is apt to be called in consultation for, let us say, the pneumonias, the fractures, or the eclampsias of his community. Because of this altogether natural process of selection even the practitioner, unless he happens to be covering his district single-handed, comes inevitably to particularize in his work with the passage of time.

A medical schools to realize that for the practical requirements of the family doctor there is too much early teaching without a hint at its application, and should it lead to such a modification of the course that the prospective patient and his malady are in the student's mind and before his eyes at least for an hour or two of every day for four years instead of a scant two, society would greatly benefit, and there would be less reason to complain of the high costs of doctoring. There is every reason to believe that out of this system there would emerge just as many capable investigators who choose to devote their lives to research, just as many who feel the urge to strive for an academic career in clinical medicine, and just as many future leaders in the public health service as we produce by the curricular program of isolated compartments now in fashion.

The physiologist complains, probably with some justice, that the principles he has laboriously taught are not sufficiently dwelt upon at ward rounds; the pharmacologist, that therapeutics is neglected; the bacteriologist, that not enough stress is laid on allergy to which a new journal is entirely devoted; and now pressure is being brought to bear to have all bedside teaching permeated with emphasis laid on *prevention*, as though this were something novel to the clinician.

A rose by any other name is just as sweet, and there has been in common English usage for the past four hundred years what the doctor has known as prophylactic (to keep guard before), meaning precautionary, medicine. And it would be a slur on the students' intelligence for a surgeon, let us say, to point out, as he has been urged to do, that he wears rubber gloves to "prevent" infecting the patient, gives the anaesthetic to "prevent" pain, removes the appendix to "prevent" peritonitis, and so on, *ad infinitum*. For his own part, he sits down and has a cup of tea to "prevent" fatigue and then to "prevent" irritation keeps away from the faculty meeting where the great importance of preventive medicine will again be pointed out to him. Like many another catchword—"reconstruction," for example, which was on everyone's lips after the War—"prevention" can be very much overworked. There is only one ultimate and effectual preventive for the maladies to which flesh is heir, and that is death. Whether we have temporarily overstressed science and research in medical education and let it come to enslave us is not for anyone to say.

If it has, the day will arrive when of itself the pendulum will swing and there will be a corrective reaction, for there usually is to whatever we overdo. In France, as all know, the traditional method of instruction has been all too much the other way about, for it has long been the custom there promptly to souse the matriculant in the sea of disease from which he must flounder his way out. This he has managed somehow to do. But now the pendulum swings and there has been, as here, a much discussed movement to reorganize medical teaching to meet the demands of the changing times. Not only is it proposed to add an extra obligatory year to the medical course, making six to qualify for general practice, but two years more than that will be required of those who would take up a specialty, and when it comes to those who aspire to be operating surgeons—so dangerous to *ses concitoyens*—an additional four years.

Even this is not all. The matter has reached and been ardently discussed in the Chamber of Deputies where the desirability of more scholarship and less science for the practising doctor has been warmly advocated. A "Back to the Humanities" movement has arisen which would oblige the prospective medical student before his matriculation not only to be qualified in preliminary physics, chemistry and the natural sciences, but since all good things are of Hellenic origin, he must know Greek and Latin as well!

There meanwhile has been much pointing to Sir Thomas Browne and to Rabelais and to the Linacres of the profession, as though many of us could hope to be humanists of their sort, any more than be productive investigators in the fields of present-day medical science. And while it is a subject on which a surgeon, in view of his illiterate ancestry and addiction for the vernacular, is scarcely entitled to speak, he can at least be permitted to admire and envy scholarship in his medical colleagues—even as did Paré.

Professor S. E. Morison, the historian, has called my attention to the fact that at Harvard, and probably at other universities as well, medical *Questiones* in past years were publicly debated in Latin at Commencement. In 1660: *An Motus sanguinis sit Circularis?* (Is there a circulation of blood?) In 1678: *An hepar sanguificet?* (Does the liver make blood?) In 1687: *An Curatio per pulverem sympatheticum sit licita?* (Can a cure be effected by sympathetic powder?) In 1690: *An Morbi sint Contagiosi?* (Are diseases

contagious?)—and so on, showing that seventeenth century laymen were interested in matters concerning which contemporary doctors, trained by the apprentice system—and not a bad system at that—were inclined to disagree.

And even at the present time, I believe that the translation of a page both of Greek and of Latin is still required of everyone who would become Fellow of the Royal College of Physicians and thereby qualify as a consultant—for how else could he use the pharmacopoeia and write prescriptions, much less read the *De Motu Cordis* in the original! I was once told by Sir Henry Head that in 1900 when both he and the late Robert Bridges had gone up for their fellowship examination together, they chanced to meet on leaving the hall and he asked Bridges how he had made out with his translations. Bridges replied that the stupid examiners hadn't stated what language they wanted the pages turned into, so he had translated the Latin page into Greek and the Greek into Latin.

There always have been and always will be a certain proportion of scholars and humanists in Medicine—men like William Sydney Thayer who has so recently left us—just as there will be a smattering of scientists and artists and musicians, even novelists, poets, and an occasional statesman like Clemenceau—and it will be a sad day when we all come to be cut from precisely the same piece of educational cloth. Some may happen to take their scholarship, as others pursue their hobbies, seriously, even professionally, but the curriculum has less to do with it than most of us pretend to believe.

Where now do we stand with the case before us? Sir James Paget once remarked that so far as he could learn, he was the only person who had ever recovered from double pneumonia after nine different consultants had been called in on the case. Dame Medicine finds herself just now in a similar plight. Considering her age, she has been unusually active these past few decades, and much to her embarrassment finds herself as "news" and altogether too much in the limelight. Being a retiring person who prefers simplicity, she has begun to show the strain of justifying the luxurious Babylonian hospitals and laboratories people of inflationary tendencies have insisted on building for her to use and give her whole time to.

Meanwhile, she has been somewhat worried by the fact that

altogether too many of her offspring under the influence of the saxophone and the speak-easy have gone distinctly modern, become citified, ticker-minded, and gotten out of hand. While she has tried to console herself with the thought that this was only a temporary post-bellum phase, which seemed to affect other people's children the same way, her personal responsibility in the matter was put in the hands of a Commission of nineteen eminent persons for investigation. After giving them what help she could and hoping an explanation for the existing instability of the world would be found, she set about her daily tasks with customary energy and apparent good spirits.

But the real trouble began after someone persuaded her five years ago, when she was feeling sturdy enough, to submit to a physical examination—in fact, considering her recently recognized social importance, her countless dependents and retainers, not to speak of her immediate family, she should have done so of her own accord every six months at least. Why, with all her hard work these past years she probably has hypertension or something worse, which should have been taken in time!

In view of her long neglect, it must now be done thoroughly and scientifically—family, marital and past history, social environment and habits, dreams and complexes, just to start off with. High blood-pressure indeed! Why, one couldn't prick or prod her anywhere without finding a sore spot. Whatever the cost, she must take a room in the medical centre for a more detailed study.

With misgivings, to this opinion she reluctantly submits. A board of fifty consultants composed of experts and specialists of every sort is called in. They in turn appoint others to assemble the data necessary for a diagnosis. Surveys are made, statistics are gathered and graphs plotted. Twice a year to discuss and correlate the findings, the chief consultants meet, meanwhile issuing reports of progress; and being scientific rather than practical doctors, the patient is not only allowed, but encouraged, to read these protocols; and she begins to feel very shaky about herself.

It becomes perfectly evident that the family, after a fair start, has somewhere acquired a bad gene—possibly from that fellow Paracelsus. And the poor old thing has had altogether too many offspring, most of them turned loose with no sort of control. These past few months, she's not only been losing weight but showing signs of irritability and certainly should be psychoanalyzed. This

so far she has flatly refused, saying it's nasty; so we must keep her in bed a while longer, perhaps a wheel chair for an hour in the afternoons, while further studies of these alarming symptoms are made.

One of her doctor sons, who for propriety's sake has been permitted to sit in with the consulting board as an observer, occasionally slips into the sick-room, pats her on the back and says: "Never mind, Mother, buck up, it will soon be over; there's not much more they can find to do, and I'm sure it's not so bad as they think. Even if it is, you've had a good fling these past forty years and the boys have asked me to say how sorry we all are not to have been a greater credit to you. But you simply *must* stop reading your clinical history and watching your temperature chart, you'll get neurasthenic. What you chiefly need is a good night's sleep."

Finally the data are all prepared; and as usual, there is want of agreement on the diagnosis and much less, consequently, on what's to be done. The gloomy majority feel that it's a deep-seated disease and probably incurable, but birth control and a better distribution of her activities in thinly populated places might be worth trying; but before it's too late, she certainly should get insured. The more cheerful minority, who know her better, think it's just a case of nerves brought on by the times, by over-work and needless worry about some of her unruly children. One or two others, disagreeing with both of these opinions, insist that, nothing venture nothing have, it's better to be bold and operate at once as it's the only possible way to make certain there's nothing in the pelvis—and if there isn't, there likely enough won't be.

As a compromise, someone is told off to break it to the poor old thing, considerably shattered by this time and a shadow of her former confident self, that though there is something indeterminate which is radically wrong, she may temporarily leave the clinic, on payment of the bill—now amounting to several millions —which she will find at the main office. However, if she doesn't change her general habits and manner of life, which make her a menace to society, and adjust herself to what is now an industrial world dominated by business and insurance, she'll be obliged to return for an exploratory operation, and that will cost a pretty penny.

Whereupon, with thanks for their efforts on her behalf, she ventures to suggest that everyone seems to be suffering just now from a sense of insecurity and indecision and it might be as well to wait until we pull ourselves out of this present slough and see just where we persons of modest means all stand before deciding on anything radical. She calls to mind what Galsworthy once said: "the *statu quo* is of all things most likely to depart; the millennium, of all things, least likely to arrive." There might chance to be a war or another influenza epidemic when we would need all the doctors we have and more, and all the empty hospital beds would quickly refill.

There are two sides to every question and inability to see both constitutes the fundamental weakness of all theories and particularly those relating to the biological and social sciences. This failure even invades what is supposed to be the most exact of all sciences, astrophysics, which supposedly deals with great abstracts. But one can approach an abstract from either side, and depending upon different views of cosmogeny, the universe is either expanding at a terrifying rate or contracting no less rapidly. If both views are correct, it must therefore pulsate like a macrocosmic heart.

But however this may be, those who deal with the science of society deal with something that actually *does* pulsate with so short a time cycle that conditions almost from year to year are never quite the same, so that our theories of today are likely to need modifying tomorrow. What this puzzled world needs perhaps is more study of the past, fewer commissions and surveys of the present, and a greater number of philosophically minded, self-supporting and law-abiding persons who can see all round their particular problem and independently devote themselves to it as do most doctors and as did the little knife-maker in Langres.

And should the doctor, in moments of discouragement about the shortcomings of his own tribe, now so thoroughly ventilated as to make those he is most anxious to help have misgivings about him, need like other people a timely word of comfort, he can remember that, whatever the doctor of the future may come to be, it has been said not long ago of the doctor of his particular time—and with some small measure of truth by one who had good reason to know him well—that:

He is the flower (such as it is) of our civilization; and when that stage of man is done with, and only remembered to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race. Generosity he has, such as is possible to those who practise an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarassments; and what are more important, Heraclean cheerfulness and courage. So it is that he brings air and cheer into the sick-room, and often enough, though not so often as he wishes, brings healing.

THE FEMALE SEX HORMONES

THE PRESENT STATUS OF OUR KNOWLEDGE OF ANTERIOR PITUITARY FUNCTION

HERBERT M. EVANS, M.D.
Berkeley, California

Physiology of the Anterior Hypophysis

I Introduction
II The Growth Hormone
III The Gonadotropic and Lactogenic Hormones
IV Respiratory Metabolism and the Thyreotropic Hormone
V Adiposity
VI Carbohydrate Metabolism and a Diabatogenic Hormone
VII An Adrenalotropic Hormone
VIII Conclusions

Mr. President, and members of the Congress, you have honored an investigator from a remote western university by the opportunity to open this afternoon's symposium devoted to one of the most dramatic chapters in the progress of modern medicine—the story of the evolution of our knowledge of the pituitary body, that minute glandule situated almost in the mathematical center of the head, regulating, as it does, those fundamental mechanisms of growth, reproduction and even the power of the body to control metabolic machinery. The story, too, is only typical for what may be told of other parts of the endocrine mechanism of the body, so that I trust, Sir, that this meeting of the Congress of American Physicians and Surgeons may gain significance in the future as having marked a turning point in the kind of interest displayed toward certain fields of medical research.

We are conceivably at the inauguration of a new era, an era which shall witness the same startling disclosures and conferring upon us the same beneficent instruments of prevention and control as characterize what I may term the bacteriological epoch, so gloriously inaugurated by the labors of Louis Pasteur and Robert Koch. Endocrinology, which suffered obstetrical deformation in its very birth by the extravagent claim of the septuagenarian, Brown-Sequard, that he had magically restored his youth with testicular substance, has continued to suffer the same sort of obloquy through similar claims of the modern Steinach school,

whereas to be an endocrinologist among the practising profession to-day means too often to be primarily concerned with making fat ladies thin. In research, matters are hardly better. No institute of any importance devoted to medical or biological research has concerned itself wholly, or even partly, with the field of the endocrines, and few university departments have done so. Yet, this kind of inquiry has given medicine the greatest single new therapeutic achievement in our day—the discovery of insulin. And the domain of endocrinology, both for clinical study and for laboratory investigation, affords a realm, where in many places, exactitude in observation and quantitative results may be secured.

It is of special significance, too, Sir, that you* preside at this meeting. It was you who had the courage to attack the problem of the essentiality or non-essentiality of the pituitary gland to life itself, and to show error in the claims of the Roumanian surgeon, Paulesco, that following complete hypophysectomy death must inevitably supervene. It is to your early efforts that we owe the first experimental production of the adiposo-genital syndrome in animals—it is to them that we owe the earliest inquiry into the upset of carbohydrate metabolism which is so thrilling a chapter in the narrative of current discovery, so that quite apart from the production by you in 1912 of a clinical monograph[1] which shall forever be a landmark in this subject, we owe a continuous series of studies in the physiology, normal or disordered, of the pituitary, the most recent, but surely not the last of which is your recognition of the clinical syndrome furnished by basophilic andeomata[2]—studies so comprehensive that with them alone my whole brief hour here could be abundantly concerned.

To the historian of science it will perhaps appear remarkable that so long a time was consumed by the period of indecision as to whether the hypophysis was or was not essential to life: he will, of course, be aware of the fact that in this epoch surgical technic was in full possession of asepsis, anesthesia and the control of hemorrhage, and had not hesitated to enter the calvarium, succeeding for instance, in the difficult removal of brain neoplasms and other intricate procedures.

To what then may we attribute so long a dispute as that waged by skilful experimenters over the dispensability or indispensability

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* Reference is made to Dr. Harvey Cushing, President of the Congress.

of the gland? This may be attributed to two causes: first, to the deaths which mysteriously followed within a few days the operations of very skilful surgeons where the complicity of hemorrhage and of infection were eliminated but where we now know brain injury was inevitable, and secondly to the tardiness with which the few successful experimenters furnished that indubitable proof of complete removal given by subsequent sacrifice of the animal and microscopical exploration by serial section of the whole contiguous base of skull and brain; persisting fragments are now known to exercise a beneficent influence which is outstanding. As regards this point, twelve pieces of research have now adequately furnished the criteria essential for establishing the fact that no portion of the hypophysis is essential for the continuance of life itself.

As regards the first point, in spite of great skill, misfortune attended those early investigators who chose a dorsal or lateral temporal opening of the calvarium from which the singularly deep hypophysis is hardly accessible without contusion of the brain. Thus the features of that syndrome once designated as cachexia hypophysiopriva were really all due to the almost unavoidable brain injury and none of them to injury to the gland itself.

Approach from below, through the sphenoid, either through the nose, mouth,[3] or pharynx,[4] especially in forms like the rat where the cavity of Turk's saddle is not only well separated from the cavum cranei by the diaphragma sellae but where the pituitary is fortunately not firmly attached to its sheath and can be aspirated without traction on or rupture of the diaphragma, or again, the clever use of Weed's contrivance for physiologic "shrinkage" of the brain by intravenous hypertonic salt solution have enabled a considerable and growing number of operators to remove the whole gland in a high proportion of all cases without immediate post-operative fatalities. The achievements of Smith,[4] Dandy and Reichert,[5] Reichert,[6] Van Dyke and Wallen-Lawrence[7] Pencharz,[8] Selye,[9] and others, have answered in the negative once for all the question as to imminent death from removal of the pituitary. Complete removal of the gland is compatible with the continuance of life. Future research will sustain us, however, in stating that it will be possible to prove that mal-effects from ablation occur immediately and continue to grow graver, even though they do not, for a considerable time imperil life.

Complete ablation of the gland *invariably* leads to a serious abnormal state, variously tolerated by various individual animals. Some long survivals and many moderately long ones have been secured by the investigators mentioned. *Most* hypophysectomized animals, surviving the operation, succumb from this cachexia before anything like a normal life span has been passed. It can be confidently predicted that the marked limitation in the life of hypophysectomized animals will become apparent as soon as we have even approximate statistics as to the fate of large numbers of such animals under ideal conditions, i.e., when submitted to no subsequent procedures and surrounded with every hygienic care. It cannot be said that investigators have intentionally obscured this truth by failure to publish such mortality tables—they have merely had more immediate duties—they have wisely employed such animals in various physiological tests involving risk, and they have intentionally sacrificed most of them for study.

These surgical triumphs have, in a way then, closed one era of experimentation in this field, but in a more important sense they have inaugurated another one, for they have now furnished us with the most conclusive test objects conceivable, for replacement therapy—the only final answer as to whether we have, or have not, in extracts, captured all the essential chemical substances furnished by the gland.

The Growth Hormone

The condition produced by complete removal of the hypophysis is, as has been explained, an abnormal one, although adult animals, except for genital regression, may not for some time show external deviation from normality and thus disguise the fact that both structure and function of the body have suffered serious change. Moreover, it is a safe prediction that as increased analysis of the bodily mechanism of hypophysectomized animals is made, other features of the state which can be strictly designated *cachexia hypophysiopriva* will increasingly come to light. On the other hand, when the gland is removed from young animals, the most impressive evidence that we have interfered with normal processes is soon furnished in their failure to grow.

If the anterior lobe has been completely removed, growth stasis is almost, if not quite, absolute, and careful post operative registration of body dimension and lines by the measurement of

skiagrams (Dandy and Reichert, Reichert) will bring conviction here. It is indeed only in this way that proof may be secured of the totality of the removal. The growth stasis carries with it also the survival of the *status quo* as far as the child-like proportions, and many, if not all, of youthful structural peculiarities, such as the possession of only milk dentition, the characteristically fine (lanugo) hair coat, and open epiphyseal cartilages. Yet this state is hardly the desirable one of "perpetual youth" for the capacity of the body in many measurable ways has been injured. Nor, structurally, have we permanent youth, for we now know that many abnormal anatomical changes begin to slowly intervene—changes which mark off these dwarfs as peculiar—e.g., the actual shrinkings of the epiphyseal cartilages, the gradual obliteration by dentine of the pulp cavities of the incisors (Schour),[10] etc. There seems no question but that we have to do with a disturbance of calcium metabolism after hypophysectomy, as reflected in the decreased calcium content of the blood; whether this is due to the correlated subnormality of the parathyroid glands remains to be established. Changes in the parathyroids as a result of hypophysectomy have not been adequately studied as yet. It is difficult to view the cessation of growth of the skeletal system as essentially due to disturbance in the inorganic metabolism; it is more justifiable to refer it to a singular failure in cartilage proliferation in the epiphyseal discs, and, of course, the dwarfism is participated in by all the organs and tissue of the body. Yet the experimental production of hypercalcemia in hypophysectomy by means of parathymone has not yet interested any experimenter.

To what extent have the growth defects of hypophysectomized animals been remedied by the conveyal to them of growth hormone? To a complete extent. In the cases of very great numbers of hypophysectomized dwarf rats and in several hypophysectomized puppies, completely normal stature or stature slightly in excess of normal has been thus obtained. Reichert's work with hypophysectomized puppies warns us that such growth hormone extracts must be free of gonadotropic effect else the provocation of sexual maturity may be associated with epiphyseal closure and the cessation of growth.

Hypophysectomized animals are enormously more sensitive to growth hormone than are normal ones and they thus constitute the test material par excellence for quantitative measures of the

growth hormone in extracts. But since they are not easy to produce in large numbers or to maintain in good health, it is fortunate that satisfactory growth tests[11 12] can be carried out by administering growth hormone to certain mammalian forms, where, though adulthood is reached, epiphyseal closure is singularly delayed and power to grow under stimulus retained for most of the span of life. I refer to rats and mice. Like some of the lower vertebrates, fish and the turtles, the rat grows almost throughout life but it does not do so with anything like a uniform rate. Though its epiphyses are open the adulthood is indicated by a sharp change, even if not a halt in the growth rate, and by very slow accretions of body substance after that date. We are always safely past this knuckle of the growth curve by the fifth month of life in the case of the female and the seventh month in the male, and we now use just these animals on which to confer by our various extracts unusual growth. That this growth is not adiposity, but is participated in by all the tissues of the body, is shown by *x*-rays of the skeletal system and the chart of their various organ weighings. The point I wish to bring out at present is that in our modern efforts to get the growth hormone in pure form we no longer feel compelled to treat the animals for many weeks or months, but select animals at any time between the fifth and ninth month of life, when they are on the so-called growth plateau. We follow the accretions of their body weight at five-day intervals for three or four weeks, and, if an approximate plateau can be demonstrated for an individual to call it a satisfactory test animal, we convey to it intraperitoneally the supposed growth-stimulating extract. In the case of impotent solutions, no significant growth results, but with potent solutions sooner or later an outspoken response is met. We are in this way forced to observe animals in the pre-experimental period merely for three weeks and in the experimental period for three weeks. Hundreds of test creatures can be stored and when their time comes easily observed and studied in this simple way.

The production of gigantism has not been limited to the rat. It has not been difficult to produce it in the dog, where, however, knowledge of the status to be expected in a pure genetically known strain must be insisted upon. In such a strain of pure bred dachshunds, where moreover we had litter-mate brothers and sisters, we have in five months produced monstrous animals;[13] they are not only much greater in size and weight than their controls, but

already show peculiarities which we expect to continue when epiphyseal closure determines the cessation of growth of the long bones. I refer to specific widening changes in the skull and to overgrowth of the skin shown in remarkable ring-like folds about the legs and in the head and neck which almost close the eyes and produce lap-like appendages to the cheeks or jaws. The American anatomist, Stockard,[14] prophetically assigned these skin changes seen, for instance in the Saint Bernard, but not in the Great Dane, to acromegaly, though at the time of his statement last spring, no one had as yet produced them. Three years ago, Putnam, Benedict and Teel[15] of Cushing's laboratory, reported acromegalic changes in an English bull treated for over a year, but in this form they had unfortunately chosen a skull type already distorted by chondrodystrophy, and in which, therefore, their end result presented the effects of two disorders. The changes we have provoked in the face and long thin head of the shepherd, by administering the growth hormone, whereby a grotesque shift to a caricatured blood hound has been produced, enable us, I believe, to state that for the first time we have produced specific changes by administering a specific agent to a form in which these changes never normally occur.

You will ask to what degree of purity has the growth hormone been brought? Now it is easy to produce a white hygroscopic powder stable for months at room temperature, in dry, air-exhausted chambers and capable of producing maximal growth in adult female rats in doses of considerably less than half a milligram per day. They have almost 15 per cent of nitrogen in the form of protein or a protein-like body, and it is difficult to further break them down without losing efficiency. *It appears that just as they are proving helpful in the isolation of enzymes, selective adsorption methods will be of great importance here.*

The Gonadotropic and Lactogenic Hormones

Most impressive, perhaps, of the changes caused by removal of the pituitary is the failure of development of the genital system in hypophysectomized youths and infants, indeed the regression of the system in adults—whether male or female. The testicles shrink to vestigial structures in which the atrophic tubules while never free from spermatogonia no longer contain the four cells layers of epithelium; the accessory organs (prostate, seminal vesicles, Cowper's glands, etc.) are minute; in the female similar recession of

the uterus, tubes and ovaries ensues, but microscopic examination of the ovaries shows fairly abundant primordial ova and young follicles, overtaken, however, with atresia before any considerable enlargement has taken place.

While then, clearly in the female, and also in the male, it is impossible to say that all germ cells have disappeared; and while, as we shall presently recount, germ cell production can be reinvoked in such animals by the conveyal to them of the "sex" hormone of the anterior lobe, the growth and maturation of germ cells are absolutely in abeyance; and, furthermore, that other activity of the gonads—both male and female—their endocrine, as well as gametogenic activity is suspended. We refer to the internal secretions—from whatever gonadal tissue they spring—which are responsible for the production of the male and female true sex hormones and their secondary sexual characters and characteristics. These animals show no more structural evidence of their sexual dimorphism than were present at the time of the operation and never manifest any sex interest or desire.

Just as the antithesis of dwarfism can be produced by the gigantism of hyper-pituitarism, so also a similar antithesis exists as regards the sex hormones in the anterior hypophysis, for here also the sexual infantilism seen after ablation of the hypophysis can be contrasted with a stimulation of the organs of sex by conveying hypophyseal tissue or hormones to animals, be they infantile or adult.

The circumstances which have led up to the detection of the sex hormone of the hypophysis are interesting in the extreme.[16] In the spring of 1926 Zondek and Ascheim of Berlin, seeking to influence the imature genital system in rodents (rats and mice) by various endocrine products and implants of endocrine tissues, happened to introduce bits of anterior hypophyseal tissue, to find the complete establishment of sexual maturity in these infants in from three to five days. In the same year and without knowledge of the Berlin experiments, which were only mentioned, in the briefest possible way in a note in the Klinische Wochenschrift, Smith[17] of our laboratory, made the same discovery. Just as it is possible to extract the growth hormone from the hypophysis, so now we can extract the gonad-stimulating hormone from hypophyseal tissue. Though there is some evidence of corresponding stimulation of the youthful male gonads, it is the ovary which gives a speedily

ascertained and unassailable picture of this effect, for large follicles and above all, corpora lutea appear there for the first time.

Another, and more convenient source of this hormone, however, was thought to have been discovered by Ascheim and Zondek[18] and the circumstances of its discovery are dramatic. During pregnancy, for reasons quite unknown to us, the oestrous hormone, or folliculin is produced by the body in great quantity, at a time indeed, when, according to our very limited ideas, physiological demands for it must be non-existent. It was encountered by Loewe, Laqueur, Zondek[19] and others in great quantities in the full-term placenta and finally also in very considerable quantities in the blood and in the urine of pregnant women. Now it has been known for many years that the hypophysis was strangely enlarged in pregnancy, though the cause for that enlargement has been obscure. What more natural thing to search, not only for the ovarian, but for the hypophyseal sex hormone in the fluids and tissues at the time of pregnancy. It also occurrs in great abundance at this time in both the placenta and in the urine and in contra-distinction to the ovarian hormone occurs so early in pregnancy as to constitute the means of recognizing conception, as soon as the first missed period has occurred; 21 days after coitus, a diagnostic possibility not hitherto possessed by us at so early a date. An unique advantage has accrued to us through the occurrence of this hormone (prolan) in the urine, where, normally, much contaminating protein is absent. The ovarian hormone admixed with it can also be practically all withdrawn by virtue of its greater solubility in organic solvents, ether, etc. By devices of this sort, over two years ago we easily obtained colorless solutions of this urinary hormone, protein free and almost nitrogen free which could be reduced in vacuo to a white powder and stored at low temperatures to be redissolved later. Our tests of its efficacy tally with those of Wiesner. In the purest form in which it is routinely prepared in our laboratory it can produce effects in young rodents in a total dose of two milligrams. Two claims of crystallization of this substance have recently been made. *This is not the sex hormone of the anterior hypophysis.* Our capacity to distinguish this particular substance—*prolan*—also a hormone—from the true sex hormone of the hypophysis rests on clear evidence, presently to be detailed, on a characteristic difference in the biological effects worked by prolan and by the true anterior hypophyseal sex hormone.

Origin of Prolan

No questions exceed in interest those relating to the origin and true nature of *Prolan.* Frist, as regards its site of origin, Philipp[20] and others abroad, and Collip in this country have championed the view which involves its production by the placenta. The cases presented by genital carcinoma, and especially by chorio-epithelioma whether in male or female cannot well be considered as decisive for either view. On the one hand this tissue could itself well elaborate prolan just as do the young chorionic villi (if they do) for in most cases implants of the actual tissue in question, show it housing lively amounts of prolan. On the other hand these tissues may really only store the hormone, which they stimulate the hypophysis to over-produce. Yet recently peculiar instances of the class of cases where prolan is ordinarily always abundant have been found with prolan practically absent, and they have been cleverly drawn into the support of the view of the origin of the placental origin of prolan. I refer to cases of hydatidiform mole and last month's report of a remarkable instance of ovarian pregnancy with living fetus, in both of which cases an exceedingly thick boundary zone (*durchdringungszone*)—a massive fibrin layer—interposed between fetal and maternal tissues—a zone conceivably preventing (as Robert Meyer first suggested) the diffusion maternalwards of the prolan shown by implants to be present in those membranes. The adherents of the view of the fetal origin of prolan also pointed out that in most cases the death but retention of the fetus involves the prompt cessation of the Ascheim-Zondek reaction in the urine. Nor have these investigators failed to turn their attention to the hypophysis itself. They remind us that whereas prolan is abundant in the blood and urine shortly after the first missed period, characteristic changes in the hypophysis itself, above all the appearance of the so-called pregnancy cells are not found before the end of the second month, or in primipara even later. Finally they point to the fact that the human hypophysis in pregnancy is even devoid of the hormone, as determined by the ineffectiveness of the implants.

Now I should like to call attention to recent experiments and developments which are crucial in my estimation for the hypophyseal origin of prolan; these relate to its appearance in the blood and urine of males or females after complete surgical ablation of gonads. It is true perhaps that absolute rigor of proof of

hypophyseal origin here will demand simultaneous hypophysectomy with gonadectomies, and we are involved in such a program.

Now, as regards the nature, chemical and biological of prolan, the hypophysis-like substance occurring in the urine of pregnant women—our little group of workers perhaps deserves the distinction of having first shown that prolan, while gonadotropic, is a different and less effective substance than the true gonadotropic hormone as found in the hypophysis itself. Let me enumerate the differences in biological action which have now been made out with regard to prolan in contrast to the true gonadotropic hormone of the anterior hypophysis. (*1st*) We early discovered that there is a sharp limit[21, 22, 23] to the effects which may be secured in 100 hours, by administering any amount of prolan, no matter how frequent the interval between doses given young normal immature animals (rats) whereas increasing amounts of the true gonadotropic hormone from anterior lobe tissue always give increasing effects on the genital system of the young recipients. In this way it can easily be shown that the substance in the blood stream and placenta as well as urine of pregnant women is prolan unadmixed with the true hypophyseal gonadotropic hormone. (*2nd*) Prolan is ineffective in increasing the development or weight of the testis in young birds (chicks or pigeons) (Riddle).[24] (*3rd*) Engle[25] has shown that prolan will apparently not cause reddening of the sexual skin in Macacus and related forms, whereas hypophyseal hormone accomplishes this readily. Finally (*4th*) we have shown that prolan is strikingly ineffective in hypophysectomized animals. We were able to show that even with massive doses, chronically administered, prolan may be ineffective in stirring the sexual system in hypophysectomized animals, and is always less effective than in normal ones.[26, 27] This experience led us to the conviction that the hypophysis itself must aid, in some obscure way, the action of prolan, and it led us to seek for that hypothetical substance in hypophyseal extracts. We found it abundantly present in the simple, aqueous, alkaline extracts which we were accustomed to making for securing the growth hormone; and for a time it seemed possible to us that the growth hormone itself might be transformed into the gonad-stimulating hormone. Certain only was the fact that these hypophyseal extracts conferred on prolan a strangely increased potency—a potency now comparable to or exceeding the best that could be secured in extracts of the hypophysis

containing the gonadotropic hormone itself. These facts which we designated the "activation of prolan" were quickly confirmed by other investigators e.g., Leonard,[29] and it was quickly shown that extracts of the glands, rich in the gonadotropic hormone itself and free of the growth hormone, could equally well be still further activated in their gonadotropic properties by the addition of prolan. The research of the last few months at the Rockefeller Institute, where I am a guest, has enabled us to show that this hypophyseal constituent is, however, not the well known gonadotropic hormone of the anterior hypophysis but is a body having different chemical and biological characteristics.[29] This body, the so-called "activator of prolan" when it is added to the latter, confers a stimulus to the gonads in excess of anything we have hitherto observed, save by the highly concentrated gonadotropic hormone of pregnant mare's blood serum. The new hypophyseal substance has made it possible to easily rival or exceed the maximal effects secured by the latter material and will probably prove the supreme agent for the gonadotropic therapy of the future. By means of it the ovaries of infantile rats are increased from 15 to 300 milligrams in weight and in 96 hours approach the dimensions of the kidneys of the infantile recipients.

Besides its therapeutic importance, an equally important consequence of the detection of the new hypophyseal substance is the fact that it furnishes us with an important new tool with which to recognize the presence of prolan-like bodies in the blood and urine of animals, both in pregnant and in non-pregnant conditions. And we cherish the hope—I speak of the studies of the last few weeks—that by means of this new weapon we can clear up the hitherto puzzling enigma of what seemed to be the abundance of prolan-like bodies in primates, but their absence in all other forms.

Highly interesting are the recent clear evidences of a direct relation of mammary secretion to hypophyseal influence. a field opened by the studies of Corner[30] and to which Riddle[31] has brought evidence which will soon, if it does not indeed now, convince critical workers of the evidence of another hypophyseal hormone, the lactogenic when it was discovered a few years ago that the condition of pseudo-pregnancy involved the elaboration of secreting alveoli in the mammary tree, it was settled that these things owe nothing to the presence and possible internal secretion of a fetus, extracts of which in Sir Ernest Starling's hands[32] had seemed to invoke the same response. The question was now only

which one of the endocrines was concerned in mammary development, and from the work of the Bouin school in Strasbourg it seemed likely that this could be shown to be a direct effect of the hormone of the corpus luteum. It was fortunate then that the discoverer of the lutean hormone, Corner, should have made it clear that this substance alone is powerless to achieve these effects. The story is only complicated by the fact that a structurally perfect mammary tree must be built up before the lactogenic hormone can provoke, as it does, true milk secretion.

Respiratory Metabolism and Thyreotropic Hormone

The important clinical studies of Loewe, Zondek, and of Brütt and Knipping[33] showed strikingly low basal metabolic rates in cases where the diagnosis of cachexia hypophysiopriva was confirmed by the finding of definite pituitary destruction or impairment, at the autopsy table. Furthermore a marked lowering of the specific dynamic action of food has been reported in pituitary disease especially in Frölich adiposity. (Rolly, Plant, Bernhardt.) Yet it is evident that for conviction all studies should be carried out on animals where purposeful, isolated injury of the hypophysis, without concomitant brain injury, has been made. It was only therefore when non-adipose dwarfs from hypophysectomy were available, that satisfactory studies could be made, and the work of Foster and Smith[34] represents the only critically acceptable research here and they have shown a very marked lowering of the basal metabolic rate. When the posterior lobe alone was removed, no such decrease was observed.

Highly interesting were their conclusions regarding specific dynamic action. Hypophysectomized rats fail entirely to show specific dynamic action. The authors correlate this with the invariable injury to thyroid function caused by the absence of the hypophysis, in view of the discovery by Bauman and Hunt[35] which they confirm that thyroidectomy obliterates the specific dynamic action. Now the implantation of anterior lobe alone, or of posterior lobe, did not repair this failure to respond to glycocoll but implants of the whole lobe did so. This is the only instance known to me of the synergism of the anterior and posterior lobes, so often asserted but in no other respect ever established.*

* The study of the specific dynamic effect in cerebral adiposities experimentally produced would be particularly important. Brütt and Knipping report remarkable restitutions of the effect in cases of Frölich disease by giving certain anterior hypophyseal preparations.

Four years ago these investigators showed a remarkably increased sensitivity to thyroid on the part of hypophysectomized rats, and it is of interest that the effect of thyroid was almost twice as great in hypophysectomized animals as in thyroidectomized ones. In thyroidectomized animals the increase in basal heat production caused by thyroid was about 4 times that of normal animals given thyroid, but in hypophysectomized animals it was about 8 times greater. An explanation of this has not as yet been furnished. The thyroid epithelium in hypophysectomized rats becomes reduced to the squamous type and the nuclei are flattened; the vesicles contain approximately the normal amount of colloid and possibly for this reason the reduction in weight of the glands is not so pronounced as it would otherwise be.

Subnormality of thyroid function is always evident after hypophysectomy in the very low basal metabolic rate, but it is highly interesting that complete ablation of the thyroids cannot cause so low a basal metabolism as supervenes after hypophysectomy, so that other factors contribute to produce the great lowering and the injured adrenals may contribute to it, since Ant, Froman and Bright (1922) and Zwemer (1929) have shown a fall in metabolism after adrenalectomy. Anterior hypophyseal extracts quickly restore the thyroids as determined by complete change of squamous to cubical or cylindrical epithelium and which may come to look like that of Graves' Disease; and by a rapid rise in the basal metabolic rate. The hypophyseal hormone accomplishing these results, the thyreotropic hormone, may be clearly separated from the growth hormone, for, unlike the latter, it is not completely precipitated from aqueous extracts of the gland by trichloracetic acid.

Now as we can test growth and sex hormones by their action on normal young or old individuals, so also the thyreotropic hormone can be adequately tested. In fact, convincing evidence of the existence of this hormone was first furnished by Aron[36] of Strasbourg in the rapid change it provoked in the epithelium of the thyroid vesicles of young guinea pigs. Schockaert showed that ducks are particularly sensitive to its administration, and by it for the first time produced experimental exophthalmos, an achievement recently similarly secured in the mammal by Anderson[37] of Collip's[38] laboratory and only yesterday by Marine[39] of New York.

Entirely enigmatical at present is the rather singular wearing

out of the thyreotropic effects even with the continuous administration of the hormone.

Adiposity

An important contribution has been made by Camus[40] and Roussy[41] of Paris in 1921, when they showed that adiposities with which pituitary ablations had been so often accompanied, could be produced by slight injuries to the superficial gray matter of the tuber cinerium near the hypophysis, but with the hypophysis itself perfectly intact. This story was confirmed by Bailey and Bremer, and by Smith and others. All recent hypophysectomies have shown convincingly that without brain injury one can regularly secure perfect dwarfism from hypophysectomy without traces of adiposity. The conception of a direct relation of the hypophysis to fat metabolism has hence lost caste.

In 1931 Anselmino[42] and Hoffman[43] reported the occurrence of a substance in the anterior lobe which, when injected into rats, rabbits, dogs, and human beings, causes a rapid rise of the acetone bodies in the blood. This substance is, in its physical and chemical properties, similar to the other known anterior lobe hormones; but it is separable from the growth, gonadotropic, thyreotropic and lactogenic hormones by ultrafiltration. So this principle is not identical with any other known principle. It occurs in the blood stream and has been isolated from the urine by C. Funk.

It has been found by Anselmino and Hoffman that under physiological conditions the substance appears in the blood stream only when fat is burnt. After a fatty meal, or in hunger, when the acetone bodies rise, the substance is found in the blood and can be assayed with the rat test. From different facts the authors conclude that this substance has a regulatory function in the fat metabolism. These facts are: *primarily* the physiological occurrence of the substance in the blood only when fat is burned, not under other conditions; *secondly*, the well known connection of acetone bodies with fat combustion or transformation, and, *finally*, the old clinical observation of the connection of the anterior lobe with certain forms of obesity, just recently again shown by Cushing in his new anterior lobe syndrome, basophilism. It is this group of facts, at any rate, which have induced these authors to call this substance, not yet completely characterized, the *fat metabolism hormone* of the anterior lobe.

Carbohydrate Metabolism and the Diabetogenic Hormone

That the hypophysis is related in some way to carbohydrate metabolism did not escape either experimenter or clinician, and when in the pioneer ablations of Cushing, adipose dwarfs were created, he was not surprised to detect in them an increased tolerance for carbohydrate, for this stood in his mind in proper contrast to the association of diabetes with acromegaly. However, the whole question of the relation of carbohydrate metabolism to the anterior lobe waited for its secure establishment for the series of researches by Houssay and his colleagues which was ushered in by the Houssay-Magenta[44] discovery of the increased sensitivity to insulin shown by hypophysectomized dogs, a fact which has been abundantly confirmed by Geilung[45] of Baltimore, Kobasashi, and others. But the most remarkable disclosure by the Houssay school is perhaps that relating to hypophysectomy as strangely ameliorating diabetes produced by ablation of the pancreas. The complicity of the anterior lobe here seems clearly established by their demonstration that implants of it (not of the pars posterior or intermedia) immediately bring on hyperglycemia in such animals. The detection of just which of the anterior hyhophyseal hormones is responsible for the pancreas-pituitary relation would seem possible by the study of the potency of the various extracts in reinvoking diabetes after the double operation (hypophysectomy, pancreatectomy) or of the capacity of such extracts to control the toxicity of insulin in hypophysectomized animals. Such preliminary work as has yet been done in the latter field is unsatisfactory.

The Houssay school has shown that morphine and adrenalin hyperglycemias are less in hypophysectomized animals. They have, in fact, shown that hypophysectomized animals are peculiarly susceptible to hypoglycemia from fasting alone, hypoglycemias which may prove fatal. It is strange that for so long a time these were overlooked. Pencharz with us has found the striking picture of hypoglycemic collapse in hypophysectomized guinea pigs, on coming to the laboratory in the morning and has been able to provoke a Lazarus-like resurrection with glucose, by stomach tube or needle.

We have seen that modern experimental work challenges the complicity of the hypophysis in conditions which have long been called hypophyseal adiposity. On the one hand we have seen that

adiposity does not result from the discrete injury of the hypophysis or its removal. On the other hand we have seen the production of this adiposity by brain injury in regions adjacent to the gland by Camus and Roussay, by Bremer and Bailley and by Smith and others. It is highly important then to inquire whether contiguous brain injury, in these hypophysectomies, be it ever so slight, has not actually been the true cause of the upset in carbohydrate metabolism. Possible nervous origin for such an upset has been known, of course, from the time of Claude Bernard's sugar puncture in 1858, and we know the modern studies on hypothalamic metabolic centers. Nor can sugar upset with pituitary tumors being any decision here, for a possible encroachment of the neoplasm on any of these centers is obvious. It would seem of maximal importance, therefore, for us to be able to say, that we have provoked true diabetes in normal dogs, with nervous system of course intact, by the administration of alkaline extracts of the hypophysis.[46] The experimenters would seem to possess crucial value in establishing a hypophyseal causation of diabetes by humeral channels, that is, by an over-production of one of its hormones, diabetogenic in effect. The method of action of this hormone, its possible repression of the function of the islands of Langerhans is as yet entirely unknown; nor has the separation of the diabetogenic hormone from the growth and thyroid and adrenal affecting hormones been accomplished. I can only state that the gonadotropic hormone is not involved.

Adrenalotropic Hormone

Perhaps the most deeply interesting changes as a result of ablation of the pituitary are those provoked in the adrenal; while the body weight in these dwarfs is much below that of their normal litter mate controls, an even more strikingly atrophy overtakes the adrenals. The glands as a whole not only decrease greatly in weight but are ultimately less than half, and this decrease is due to reduction of the adrenal cortex which becomes little more than a shell.

On account of the well-known essentiality of the adrenal cortex for life it was only natural that investigators should inquire as to whether the ultimate strange sickness and death of hypophysectomized animals was not due to cessation of adrenal cortical function. Hence it was that we administered Swingle's adrenal cortical

hormone to hypophysectomized animals that had begun to decline many months after the operation. This vitally important adrenal substance did not modify their decline—a decline dramatically changed to improvement the moment we gave them aqueous alkaline extracts of the anterior lobe. The sudden resuscitation which one can invariably produce in this way is attended not only with abrupt general body growth but with slower and ultimately complete regrowth to normality of the adrenal cortex. Adrenal cortical tissue therefore needs for its normality some constituent of the anterior hypophysis. Since a long series of experiments has shown that replacement of the adrenal cortex in hypophysectomized animals is never provoked even by concentrated dosage with the gonadotropic hormone[47] and since it is invariably produced by certain extracts of the growth hormone, but not by other highly purified ones, it would appear inevitable for us to recognize the existence of an adrenalotropic hormone the properties of which as distinguished from the thyreotropic, lactogenic, and other possible hormones, will emerge, I trust, from the research of the three or four laboratories devoted to this subject, in the course of the next three or four months. Concentrated preparations of the adrenalotropic hormone should enable us to more readily provoke the hypertrophy of accessory adrenal tissue after complete excision of these glands. Nor is it altogether out of the question for us to hope that the hypertrophied fragments will more readily undertake normal functioning and that Addison's disease may thus be attacked, not by replacement therapy, as is at present the case and is the case with diabetes, but by a new type of therapeutic procedure, one that will stir the defective tissue to resume its normal task.

Conclusions

In conclusion, gentlemen, I realize that the bewildered hearer of my exposition will desire to be assured of the justification for the recognition of such a perplexing number of apparently discrete internal secretory substances or hormones furnished by a bit of tissue where at most three or four distinct cell types have been recognized in modern histological research. Pending the time the biological chemist develops methods for the further concentration and above all for the complete isolation of these substances, preferably in crystalline purity, you will desire to know briefly

whether or not biological workers have perfected a methodology adequate for the identification of discrete effects. I can only state that fortunately at the present time sufficiently sensitive test objects would appear to have been found for each of the five substances—the growth, gonadotropic, thyreotropic, lactogenic, and diabetogenic hormones—and that in many cases, but not yet in all, we have assurances of relative, if not absolute, freedom from any but a single effect.

You may also challenge the assumption that these various isolated and clear-cut effects, are all the direct results each of a peculiar hormonal substance each acting on a particular end organ. Might not some of them be secondary, that is indirect effects of two or three fundamental hormones like those which govern growth and sex? Now I think that this vitally important criterion will also quickly be met. The effect of the growth hormone, is of course, general. But the effects of the gonadotropic and thyreotropic hormones have been recently shown to be exercised directly on their recipient tissues, for these secretions cause their characteristic effects when they are placed in contact with gonadal or thyroid tissue in the Warburg chamber.

Fortunately the biological chemist has now joined forces with the biologist, or in the example of my gifted follower in this symposium, Dr. Collip, has taken charge of this whole affair, and you will sympathize with the impulse that leads me to the prediction that by seizing hold of some of the most modern tools of biological chemistry, those, for instance, that have been so useful in vitamin and above all in enzyme research, ultimate identification of these substances will not be long delayed.

Twelve years ago you, Sir, as President of the Association for the Study of Internal Secretions, gave an address as distinguished for diction as you are for that combination of surgical skill and intellectual discrimination. In your concluding remarks you rightly stigmatized behavior which, if not outright charlatanism, condoned those jumps to premature conclusions that have all along worked to the detriment of endocrinology. And you said, Sir, to present an extreme. "The Lewis Carroll of to-day, would have Alice nibble from a pituitary mushroom in her left hand and a lutein one in her right, and presto! she is any height desired."[48]

I have presented you to-day with giants presenting infantile sexual systems, or with young creatures still suckling their mother

and yet themselves actually sexually mature; moreover with the experimental imitation of that South American male savage seen by Alexander Von Humboldt to be suckling his child. These mysteries, therefore, are at hand. We are not living in a dream, but have worked with exactitude and need not cry out then for deliverance from this dream, "Alice, where art thou? for it must be you, Alice, in this queerest of worlds, who hath taken us by the hand."

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CHEMISTRY AND PHYSIOLOGY OF ANTERIOR PITUITARY HORMONES

BY J. B. COLLIP

Department of Biochemistry, McGill University, Montreal, Canada.

It is my purpose in this communication to discuss the results of the experimental work upon the chemistry and physiology of the anterior pituitary lobe which have been obtained in my laboratory during the past year. My collaborators in the various researches to which reference will be made have been Doctors H. Selye, E. M. Anderson, D. L. Thomson and L. I. Pugsley, Mr. P. T. Black and Miss J. E. Williamson.

The literature on pituitary physiology is most extensive, and insofar as concerns our own work it has been reviewed elsewhere.[1] I should like to state, however, that the work which we have done is founded directly upon the earlier work of Evans, Smith, Loeb, Riddle and many others.

Contributions to Anterior Lobe Physiology

The purely physiological investigations which formed the basis for our later work on the fractionation of anterior lobe extracts will be dealt with first.

Doctor Selye devised an improved technique for hypophysectomy in the rat. His method, based upon that of Smith, has been described in detail.[2] In all, some 2,000 hypophysectomized animals have been available to us for experimental studies. The effects of hypophysectomy which have been previously described —namely, cessation of growth and atrophic changes in the gonad, thyroid and suprarenal glands—were repeatedly observed. Moreover, the rate of decline of these glands was noted, so that excellent control data became available, and these were of great value in the study of the effects of specific replacement therapy by means of purified extracts.

Experiments Relating to Pregnancy and Lactation

Hypophysectomy during the second half of pregnancy did not—

as had previously been thought[3]—lead to death and resorption of the foetuses. Pregnancy was prolonged up to 26 days and in 22 out of 24 cases the mechanism of parturition was not interfered with and the litters were born alive; in two exceptional cases haemorrhage occurred at term and the foetuses died in utero. It was observed that milk secretion always set in at birth in the animals of this series, but that it invariably stopped after a few hours, so that the mothers were absolutely unable to nurse their young. In keeping with these observations it was repeatedly shown that milk secretion stopped after hypophysectomy performed at any time during lactation.

Since there was a definite secretion of milk for a few hours post partum in the hypophysectomized rat, it was apparent that a stimulus extra-hypophyseal was acting. Doctor Selye therefore emptied the uterus in late pregnancy in 10 animals by Caesarian section and observed in this series that lactation set in within 36 hours, whereas in other series in which the pituitary was removed coincident with the removal of the foetuses no milk secretion occurred.

It had been observed in this laboratory that chronic treatment with the ovary-stimulating hormone of the placenta (A.P.L.) results in an enormous increase in the size of the ovaries (as much as 1000% in 3 to 6 weeks, with daily injections of 50 to 200 units). If the treatment is continued the ovaries return to normal size, but they do not as a rule show a normal histological picture. Coincident with the peak of the curve of ovarian weights obtained in such experiments the anterior pituitary lobe is definitely enlarged, the thyroid gland is enlarged and hyperplastic, and the mammary gland is developed as in the last few days of pregnancy. Ovariectomy in such animals has led at once to the fully developed mammary gland entering a stage of active secretion within 48 hours of the removal of the ovaries. This result was not obtained if hypophysectomy was performed in addition to castration.

Growth after Hypophysectomy

Growth ceases abruptly after hypophysectomy irrespective of the size or age of the animal except in the case of very young animals weighing less than 50 grams. In such animals slight gains (10 to 15 gms.) have been noted.

The Effect of the Ovary-Stimulating Hormone—(A.P.L.) upon Hypophysectomized Animals

The experiments of this series fall into three groups:

(1) Hypophysectomized prepubertal females

(2) Hypophysectomized postpubertal females

(3) Hypophysectomized males.

Since the results we have to report upon the effect of the placental hormone (purified either from human placenta or pregnancy urine) are at variance with certain reports of others, I should like to emphasize that we have been able to confirm our own results repeatedly.

(1) *Prepubertal females*—Daily injections of A.P.L. (40 units) has not produced vaginal oestrus. The ovaries present a smooth surface with no sign of mature follicles or corpora lutea. On section, however, nearly all the follicles are seen to have been converted into pseudo-corpora as a result of an active proliferation and transformation of the cells of the theca interna.

(2) *Postpubertal females*—Similar treatments of postpubertal females has resulted in the early manifestation (fourth day) of continuous vaginal oestrus. Experiments of this type have been carried on for as long as six weeks without any change in the picture, oestrus continuing as long as the injections were continuous and becoming interrupted upon cessation of treatment. The ovaries of such animals showed no evidence of maturation of follicles. The corpora lutea of pre-hypophysectomy ovulations were found to be well nourished.

Recently, Doctor Selye has been able to examine the ovaries of hypophysectomized postpubertal animals months after operation. In some a few corpora still persist, while the follicles have completely disappeared, with exception of a few primary Graafian follicles in the first stages of their development. In some animals, which were examined a very long time after removal of the pituitary, the ovaries have been found free of corpora. This only occurs six or seven months post-operative. In such cases, a short course of treatment with A.P.L. has resulted in the luteinization of thecal cells which sometimes was coincident with the appearance of oestrus; however, this was not regularly the case. It seems that the oestrus occurs only if the thecal luteinization reaches a very marked degree. It should be emphasized that, although the ovaries of these hypophysectomized rats increased in weight, as compared

with untreated controls, after A.P.L. administration, they never showed new corpora lutea. That thecal luteinization has never led to oestrus in the hypophysectomized prepubertal rat may possibly be explained by the fact that these animals never showed, in our experiments, such marked degrees of thecal luteinization.

In another series of experiments, A.P.L. has been given to mature rats immediately after hypophysectomy, and it was found that in these cases where corpora lutea have been present in the ovaries at the time of operation, A.P.L. has considerably prolonged their life in the absence of the pituitary. These experiments seem to indicate that, although A.P.L. is unable to form new corpora lutea after hypophysectomy, it can prolong the life of a corpus which was present at the time of operation.

(3) *Males*—The treatment of hypophysectomized males, either pre- or postpubertal, has not in any way affected the germinal epithelium in our experience. Atrophic changes in the germinal epithelium have been noted in all hypophysectomized untreated males. Treatment with A.P.L. has invariably resulted in an active proliferative process confined entirely to the interstitial tissue. Presumably this tissue produces and liberates male hormone, because the accessory organs, epididymies, prostate and seminal vesicles hypertrophy in much the same manner as is seen in normal males treated with A.P.L.

The Effect of A.P.L. in Normal Rats 6–10 Days Old

The fact that rats have not been observed to respond to ovary-stimulating hormones in the first few days of life has led to the conclusion that they should not be used as test objects for A.P.L. earlier than the 18th day of life.[4,5] In an attempt to find an explanation for this fact we injected a series of 30 rats daily with A.P.L., starting on the 6th day of life. Although no mature follicles or corpora lutea had been formed after 10 injections and the ovary did not differ macroscopically from that of an untreated rat of the same age, histological examination of this organ revealed very pronounced changes. The thecal cells were very much enlarged and assumed the appearance of corpus luteum cells, whereas the granulosa cells were not luteinized and no signs of ripening of the follicles could be detected. These experiments show that at a very early age A.P.L. is unable to induce follicular maturation or the formation of normal or atretic corpora lutea; however, it does lead

to luteinization of the thecal cells and thereby to the formation of thecal corpora lutea. These structures are not very prominent and therefore they can be readily overlooked upon macroscopic examination. Histologically they are composed of a peripheral ring of corpus luteum cells and a central part of a few rows of normal granulosa cells in the center of which the ovum is included.

It is difficult to find a satisfactory explanation for these results. The general parallelism between them and those observed in the prepubertal hypophysectomized animals is striking. There were, however, two important points of difference:

(1) Continuous oestrus occurred in the very young, normal, A.P.L. treated animals, whereas no oestrus was observed in the prepubertal hypophysectomized treated animal.

(2) The character of the pseudo-lutein cells. In the baby normal rats they were much larger and contained more lipoid material than in the hypophysectomized prepubertal, A.P.L. treated animal.

Since in the absence of the pituitary we could never induce maturation of follicles or luteinization of granulosa cells by A.P.L. we have suggested that the stimulation of the granulosa elements is only possible in the presence of a pituitary factor (the complementary substance) which would obviously be lacking in the hypophysectomized animal and which perhaps cannot be supplied adequately by the immature pituitary during the first days of life. In support of this theory we have observed that animals treated from the 6th to the 40th days of life with A.P.L. give after this time much the same ovarian picture as is seen in the ordinary Aschheim-Zondek reaction. Also, coincident with the development of follicles and true corpora lutea in such animals, vaginal oestrus has become discontinuous. From this we have concluded that the pituitary factor necessary for the full A.P.L. effect as seen in the Aschheim-Zondek reaction came into action as our baby rats receiving A.P.L. grew older.

This theory has received much stronger support from our experiments on hypophysectomized animals, both pre- and postpubertal, treated with A.P.L. in combination with small amounts of anterior lobe extracts. Typical A.P.L. ovaries, as seen in normal animals treated for 4 to 6 days with A.P.L., were repeatedly produced in hypophysectomized animals when—in addition to A.P.L.—they were injected with an anterior lobe extract (a dilute acid or dilute ammoniacal extract of anterior lobe of sheep or pig).

Control experiments, in which anterior lobe extracts alone were used, showed no such effect, but large doses of these anterior lobe extracts did produce true corpora lutea.

Evans' older observation—that prolan plus pituitary growth extract produced far greater increases in ovarian weights in normal immature animals than the sum of their individual effects—has probably the same basis.[6] Experiments with the Hisaw pituitary extract plus prolan favour the view that there is a synergism between prolan and the pituitary maturity factor.[7,8]

In Tables I to V the general type of effects which we have consistently obtained are illustrated.

TABLE I.—Control data showing effect of varying dosage of A.P.L. upon the weight of the ovaries of 21-day-old normal rats treated for 5 days.

A.P.L. Daily	No. of Animals	Body Wt. Gms.	Wt. of Ovaries Gms.
40 u.	7	36	0.036
30 u.	2	45	0.045
20 u.	2	41	0.036
10 u.	2	40	0.033
5 u.	7	43	0.033
2 u.	5	46	0.027
1 u.	5	41	0.021
0.5 u.	4	42	0.010
0.25 u.	4	41	0.012

TABLE II.—Showing effect upon weight of the ovaries of 21-day-old normal rats treated for 5 days with a purified anterior pituitary extract, alone and in combination with A.P.L.

Bi-daily Doses of Ant. Pit. C. 1 cc. = 2/3 g. A.P.	Daily Doses of A.P.L.	No. of Animals	Body Wt. Gms.	Wt. Ovaries Gms.
1/2 cc.		4	38	0.021
1/4 cc.		5	39	0.014
1/8 cc.		5	43	0.012
1/16 cc.		5	46	0.013
1/2 cc.	40 u.	4	36	0.153
1/4 cc.	40 u.	6	44	0.072
1/8 cc.	40 u.	6	44	0.046
1/16 cc.	40 u.	6	47	0.046
1/4 cc.	20 u.	6	46	0.065
1/4 cc.	10 u.	6	34	0.059
1/4 cc.	5 u.	6	44	0.039
1/4 cc.	1 u.	6	59	0.034

TABLE III.—Showing similar results as in Table II.

Bi-daily Doses of Ant. Pit. C_1	Daily Doses of A.P.L.	No. of Animals	Body Wt. Gms.	Wt. Ovaries Gms.
1/2 cc.		9	36	0.032
1/4 cc.		6	31	0.019
1/8 cc.		6	40	0.017
1/2 cc.	40 u.	4	31	0.088
1/4 cc.	40 u.	5	30	0.061
1/8 cc.	40 u.	6	32	0.042
1/16 cc.	40 u.	5	39	0.033
1/32 cc.	40 u.	5	44	0.039
1/4 cc.	30 u.	5	39	0.066
1/4 cc.	20 u.	5	37	0.074
1/4 cc.	10 u.	4	39	0.064
1/4 cc.	5 u.	10	47	0.053
1/4 cc.	2 u.	5	46	0.047
1/4 cc.	1 u.	5	41	0.042
1/4 cc.	0.5 u.	5	37	0.035
1/4 cc.	0.25 u.	5	37	0.022
1/8 cc.	1 u.	4	40	0.020
1/8 cc.	0.5 u.	4	41	0.019
Boiled 35 mins.				
1 cc.		4	35	0.034
1 cc.	5 u.	4	36	0.088
1 cc.	40 u.	4	26	0.085

TABLE IV.—Showing effect upon weight of ovaries of hypophysectomized pre- and postpubertal rats of a purified anterior lobe extract, alone and in combination with A.P.L.

Bi-daily Doses of Ant. Pit. C.	Daily Doses of A.P.L.	No. of Animals	Body Wt. Gms.	Wt. Ovaries Gms.
1/4 cc.		3	43	0.013
1/4 cc.	10 u.	4	40	0.041
	10 u.	4	49	0.019
1/2 cc.		3	124	0.040
	40 u.	2	127	0.036
1/2 cc.	40 u.	2	120	0.074

TABLE V.—Showing similar effects as in Table IV. Note that the complementary and maturity effects of the pituitary extract still persist after boiling the extract, as also shown in Table III.

Bi-daily Doses of Ant. Pit. C_1	Daily Doses of A.P.L.	No. of Animals	Body Wt. Gms.	Wt. Ovaries Gms.
1/4 cc.		4	39	0.019
1/4 cc.	10 u.	5	38	0.044
	10 u.	4	49	0.019
1 cc.		3	123	0.050
1/2 cc.		3	124	0.047
1/4 cc.		4	135	0.034
1/2 cc.	40 u.	2	114	0.075
1/2 cc.	20 u.	4	134	0.071
1/2 cc.	10 u.	3	136	0.073
1/4 cc.	40 u.	3	127	0.063
1/4 cc.	10 u.	3	89	0.029
Boiled 35 mins.				
1 cc.		5	36	0.028
1 cc.	20 u.	3	27	0.026

Our own results are open to several interpretations. Insofar as A.P.L. is concerned, we are very definitely of the opinion that a substance of true pituitary origin must work with it in order to have produced the Aschheim-Zondek ovary in the normal animal. This substance of pituitary origin might possibly be—as Leonard's work suggests—the maturity factor in high dilution. On the other hand the maturity factor may be bipartite—one part a complement inactive (in the rat) by itself; the other a substance similar to the placental hormone.

We have not had as yet a pure complementary extract of anterior lobe; that is to say, one in which even in massive doses no maturity effect has been produced. The fact that boiling our best extract has not affected its efficacy as a complement to A.P.L., nor altered its potency as a maturity substance when used in larger doses, does not help in the possible differentiation of the complementary effect from the maturity hormone.

The results of all these experiments do not, unfortunately, afford a definite answer to the vexed question as to whether the

placental hormone or the prolan of Zondek is identical with a true anterior lobe principle. However, they do prove most emphatically that the pituitary factor which synergizes our A.P.L. extract is not present in the latter. There is a very real possibility that pregnancy urine and extracts of pregnancy blood and placenta may contain, in addition to the true placental hormone, some true anterior lobe principle. Our own extracts have been notably free from this latter, but certain contradictory statements in the literature may possibly be explained in this way.

The Preparation of Purified Extracts of Active Principles of the Anterior Lobe and the Physiological Effects of these Extracts

1. *The Growth Principle:* After many trials a method was developed for the preparation of a growth hormone extract free from thyreotropic and maturity principles, but still containing a trace of prolactin.

It was first observed that an alkaline extract (anterior lobe extracted with 10 volumes of 1% NH_4OH) which had been partially deproteinized, by the addition of acetic acid to pH 6.5 and filtering, had a slight growth-promoting effect in hypophysectomized rats. Such extracts were then saturated with ammonium sulphate in the presence of 1% NH_4OH, and the resultant precipitate collected, extracted with dilute ammonia and dialyzed. After dialysis the solution was concentrated at low temperature and pressure. During the concentration process a semi-crystalline substance separated out at a pH of 7.5 to 8. This was removed and an alkaline extract of it was found to be highly potent in stimulating growth in hypophysectomized rats.

From these leads the following method has been evolved. The anterior lobe tissue is treated with several volumes of dilute alkali: 0.5 to 1% NaOH or 1% NH_4OH. The mixture is acidified with acetic acid and filtered and the residue is again suspended in dilute alkali and reprecipitated with acetic acid and filtered. This extraction with dilute acetic acid as outlined may be repeated 5 times. Ammonia is added to the combined filtrates to give approximately a 1% concentration. By the addition of appropriate amounts of calcium chloride and sodium phosphate a suspension of $Ca_3(PO_4)_2$ is produced in the solution and the whole is concentrated at low temperature and pressure until the ammonia is prac-

tically all removed. The $Ca_3(PO_4)_2$ is then collected on a Buchner filter and is extracted repeatedly with 0.5% NaOH. The NaOH solution of adsorbed material which is thus removed is acidified with acetic to pH 6.5. It is then made alkaline with ammonia and concentrated at low temperature and pressure to remove the ammonia slowly. The semi-crystalline material which separates out at a pH 7.5 to 8 is removed and extracted with dilute sodium hydroxide. The alkaline solution is then almost neutralized and it may be used for assay at this point, 1 c.c. representing approximately 2 gm. of original gland tissue. The total organic solids are between 1 and 2 mg. per gram of original anterior lobe tissue and $\frac{1}{4}$ cc. of such a solution administered twice daily to completely hypophysectomized rats has resulted in marked growth.

Physiological Effects of the Growth Hormone: Hypophysectomized rats which are treated with the growth principle within a few weeks of hypophysectomy increase in weight almost immediately, but the rate of gain gradually decreases as the treatment is continued. An average gain of 3 gms. per day is the greatest effect which has been observed. No effect has been noted upon the thyroid gland or the gonads. Some preparations have produced slight effects upon the suprarenal cortex, while others have not. This points to the presence of a small amount of the adrenotropic principle in some growth extracts. We know that the adrenotropic principle is not the growth principle, since (as will be described in further detail later) the purified adrenotropic extracts do not influence growth in themselves.

There is no change in metabolic rate of animals receiving the growth principle, but that there is a profound effect upon metabolism is well illustrated by a study of the nitrogen balance. Calcium metabolism is also favorably affected. (See Fig. I.)

The hypophysectomized animal is an excellent test object for the assay of the growth principle, since positive effects cannot be produced in the absence of the active principle, and likewise negative results are not confusing, since refractory animals are very rare. We have suggested as a unit, the smallest amount of extract which, administered twice daily for ten days, will cause an average daily gain of 1 gram in rats weighing approximately 100 grams. On this basis 100 units have been obtained from 1 gram of original anterior lobe tissue.

An hypophysectomized animal treated with the growth hor-

mone is in in no sense better off than without treatment, since increased body weight is of no significance unless the atrophic thyroid and suprarenal glands are restored as well. This raises a most interesting practical point. Growth hormone in clinical use should in all probability be used in conjunction with variable a-

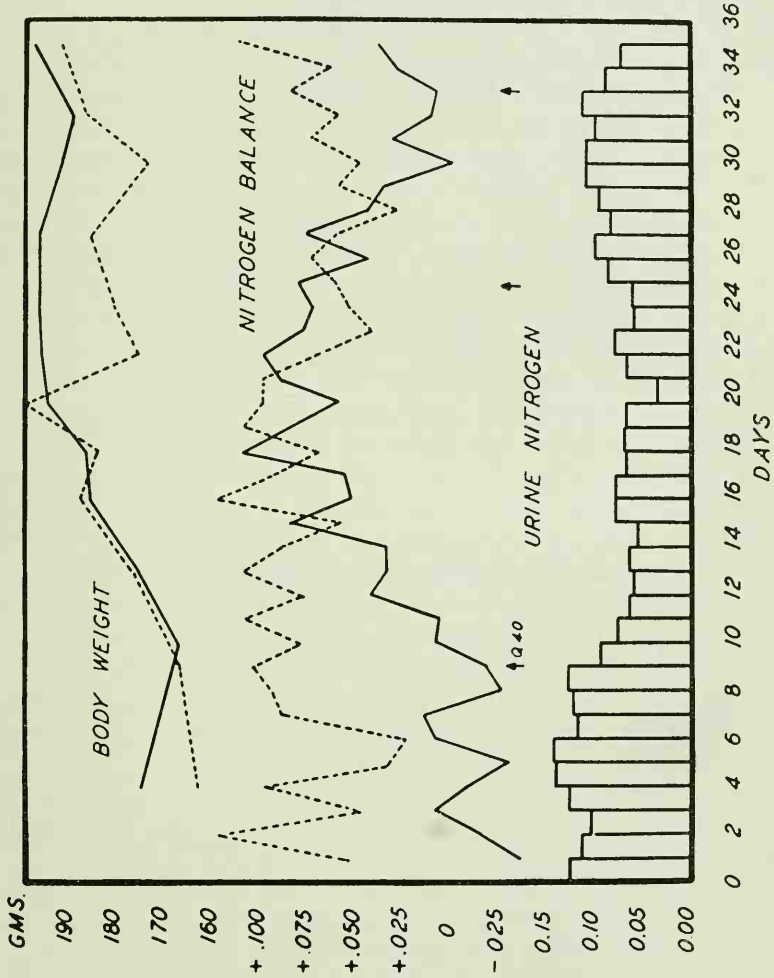

FIGURE I.—Showing the effect of the growth hormone upon growth, nitrogen balance and urinary nitrogen of completely hypophysectomized rats (solid line) and of normal animals (dotted line). At the first arrow the injections were started; at the second, injections were stopped; and at the third, they were started again.

mounts of adrenotropic and thyreotropic principles as indicated in the individual case.

2. *The Thyreotropic Principle:* The thyreotropic effects of anterior lobe extracts have long been known. In our experience, it is almost impossible to prepare a simple extract which does not contain the thyreotropic principle. When it was found that the $Ca_3(PO_4)_2$ adsorption process as used in preparing growth hormone did not remove the thyreotropic principle we set about to purify this substance from the combined filtrates and washings of the $Ca_3(PO_4)_2$ used to remove the growth principle. It was soon discovered that the thyreotropic substance was precipitated by saturation of aqueous solutions with ammonium sulphate in the presence of ammonia. Also it was noted that the thyreotropic principle was soluble in 75% alkaline alcohol, but not in neutral alcohol. The method evolved for the preparation of the thyreotropic principle consisted, therefore, in repeated precipitation from aqueous solution by ammonium sulphate and solution in and precipitation from alcohol or acetone of the salted-out material. The final product is a pure white, protein-like substance which is freely water-soluble. 1 mgm. of dry substance may contain 200 hypophysectomized rat units. Traces of adrenotropic substance are usually present in the final product, but the growth principle is absent.

Doctor Anderson has carried out extensive metabolism studies in which the physiological effects of the purified thyreotropic substance has been determined. Normal guinea pigs and normal rats of various ages have been used, but here again the most satisfactory test object was found to be the hypophysectomized rat.

The physiological effects of treatment with the thyreotropic hormone of the anterior lobe of the pituitary are of the greatest interest. These effects fall into two distinct types:

(1) those observed during short intervals of treatment, and

(2) those observed after long continued injections. These latter effects are of the greater importance.

Animals have been injected twice daily and metabolic rates taken at frequent intervals. A sufficient number have been sacrificed at various time intervals following the institution of treatment to allow of adequate correlation of the thyroid gland size and histological appearance with the metabolic rate curve. The usual metabolism curve indicates an immediate increase in rate following the beginning of treatment. The rate gradually increases

till in a week or ten days' time it is about 35% above normal. It remains at about this level for three or four days; then gradually declines to actually subnormal values in about two to three weeks. Cessation of injections at this time have resulted in a return in the metabolic rate to normal values. The same general type of metabolic rate curve has been obtained in the normal rat and guinea pig and in the hypophysectomized rat. In the case of the latter animal the control rate is, as a rule, about minus 25 as compared with the average normal animal. In these experiments the metabolic rate taken before treatment has served as a base line for the individual experiment. Doctor Anderson has frequently noted a dip in the rising curve of metabolism on the third or fourth day of treatment. This observation has been repeated so many times that it is apparently of some significance. Our interpretation of the phenomenon is that the immediate effect of the injected hormone is to cause a release of thyroxin or thyreoglobulin from the gland. The secondary effect is the production, in the course of a few days, of very definite hyperplasia with absorption of colloid. The big increase in metabolism seen after a week's time is probably due to the increased production and release of thyroid hormone by the highly active acinar cells. It has not been found possible, except under very unusual circumstances, to increase the metabolism, even with massive doses of the hormone, beyond an average of plus 35%, with a variation between plus 20% and plus 65%.

The unusual conditions referred to above, which constitute the exception to the rule, were present in the case of a small group of rats which had spontaneous goitres and which had been secured from a dealer. We are indebted to Doctor C. N. H. Long of Philadelphia for discovering these and sending us some for study. The thyroids of some of these animals weighed over 125 mgm. and presented on section a most unusual histological appearance. Little or no colloid was present and hyperplasia was so extreme as to be suggestive of early malignant change. The control metabolic rates on these animals was not outside normal limits. However, within 48 hours after thyreotropic hormone had been injected an increase of 100% was noted, and in 9 days' time readings showing increases of over 200% were obtained.

Many factors may influence the type of metabolic response to thyreotropic hormone. Perhaps the most important of these are the

size of the glands and their thyroxin content prior to the beginning of treatment.

The effects of long continued treatment with the thyreotropic hormone stand in marked contrast to the effects of short treatment. They are briefly as follows: the metabolic rate is subnormal; the thyroid gland in the case of the rat treated for six weeks may actually present the histological appearance of the gland from an untreated hypophysectomized animal, so flat and inactive appearing is the epithelium lining the vesicles which are full of colloid; the ovaries show very clearly evidence of an inhibitory influence upon them. In some cases they have been reduced almost entirely to stroma, and in actual weight to less than 20 mgm. as compared to controls of over 50 mgm.

The histological appearance of the thyroid gland of rats killed when they are still on the down-curve of metabolism presents as a rule a mixed picture. There are areas of large vesicles full of colloid and with flat epithelium, interspersed with definitely hyperplastic areas.

These effects seen after long continued treatment raise questions the answers to which cannot be given with certainty at this time. Does the thyroid gland develop an immunity to the injected hormone? Is some inhibitory mechanism brought into action by the continued stimulation with the thyreotropic hormone? Does the purified extract used contain as well a true inhibitory principle which has a definite latent period before its effects become manifest? Is the thyreotropic hormone itself an inhibitor of the ovary or is there a separate principle also present in the extract which is definitely antagonistic to the ovary?

We are inclined to attribute the inhibition of the ovary to a direct action of the thyreotropic hormone, since this effect does not develop to any marked degree until long after the thyroid stimulatory effect has passed off. The negative phase of the thyreotropic extract on the thyroid we do not feel can be explained at the moment.

A somewhat analogous case exists in connection with the inhibition of growth so frequently seen when large doses of thyreotropic hormone are administered. This inhibition of growth in the case of normal animals does not persist for more than two weeks. This would coincide with the beginning of the negative phase as far as the thyroid gland is concerned.

We have frequently noted that the growth stimulated by our "Q" extract (growth principle) could be definitely inhibited by the simultaneous injection of a simple acid extract of anterior lobe tissue of the ox; or, what amounts to the same thing, certain simple alkaline extracts containing both the growth and the thyreotropic principles have shown a latent period of ten days to two weeks when injected into hypophysectomized rats insofar as the induced growth response was concerned. Since the same result has been obtained with the purified thyreotropic extract we are inclined to look upon inhibition of gonad and inhibition of growth as active processes in which the thyreotropic principle is involved. This argument is, we feel, in no way contradictory of the view that a certain degree of thyroid activity is beneficial to growth.

The thyreotropic hormone has been found by Doctor L. I. Pugsley to cause a marked increase in the creatine excretion of normal rats. This increased excretion following bi-daily injections of the purified extract was found to reach a peak on about the fifth day of treatment. In the course of fifteen to eighteen days creatine excretion returned to normal values in spite of continued injections of the hormone. The curve of creatine elimination followed very closely the curve of metabolism. Creatinine excretion was not appreciably affected. Hypophysectomized rats treated in a similar manner gave a response similar to normal rats. Doctor David Barr has reported to me his observation of creatinuria in a human subject who had been treated with the thyreotropic hormone prepared in this laboratory. The effects of the thyreotropic hormone upon creatine metabolism are undoubtedly related to increased thyroid activity, since similar effects have been observed in normal animals fed on thyroid substance.[9,10] The adrenotropic or growth hormone fractions were found to be without effect upon creatine excretion.

3. *The Adrenotropic Hormone:* In our studies of the effects of thyreotropic extracts upon hypophysectomized animals we frequently saw that the suprarenals were restored to normal or towards normal when the atrophic thyroid glands had been brought back to normal or even made hyperplastic. This effect upon the suprarenal was not so evident as the purity of the thyreotropic fraction was increased. Extracts prepared from the alcoholic mother liquors from which the thyreotropic principle had been largely removed were found to be excellent in adrenotropic activity. Finally, from a 75% acetone-soluble fraction we obtained,

on concentrating at pH 5 to 6 in the aqueous phase, a fine flocculence. This was removed, dissolved in dilute ammonia, the ammonia removed by vacuum distillation, and the extract tested at this stage on hypophysectomized rats. It proved to have no thyreotropic activity as judged both by its failure to raise the metabolic rate and its failure to restore the atrophic thyroid gland. It did, however, restore the suprarenals to normal in the course of one week. It had no growth effect, nor did it contain any maturity factor or complementary substance. It is in fact as pure a pituitary extract as we have been able to obtain. Daily injections of $\frac{1}{4}$ mgm. of the dry substance was sufficient to restore the suprarenal cortex to normal in hypophysectomized rats in which the atrophy of the cortex was previously proven by biopsy.

4. *Prolactin:* We have confirmed Riddle[11] in his observations relating to a pituitary fraction which will induce crop-gland milk secretion in the pigeon. We prefer to use an alkaline extraction process to prepare this substance. We agree with Riddle that the "prolactin hormone" is not identical with either the growth, the maturity or the thyreotropic hormone fractions.

5. *The Diabetogenic Principle:* The remarkable fact discovered by Houssay,[12] that an hypophysectomized, depancreatized animal has little or no diabetes but can be rendered markedly diabetic by the injection of anterior lobe extracts, raises the question as to whether there exists in pituitary extracts a truly diabetogenic principle or whether this property is shared by one or other of the known active principles.

Doctor B. O. Barnes,[13] who has confirmed Houssay's work, has been kind enough to test some of our extracts for the diabetogenic effect. He has obtained positive reactions with both the growth and the thyreotropic fractions. The relationship of the pituitary to carbohydrate metabolism is one of the most interesting and important subjects in the study of anterior pituitary physiology, but it is one upon which we have not as yet sufficient information to allow of proper orientation.

In closing, I should like to raise the question as to whether the various physiologically active substances which can be obtained in individual extracts of anterior lobe tissue are true hormones. It may be possible that the number of true hormones in the living gland is very limited; that, in the process of extraction where conditions are such as to favour mild hydrolytic processes, certain

active groups are released from a master protein molecule; and that in the further process of purification of physiologically pure "hormone" fractions these active substances are in very large measure separated one from the other.

While the laboratory work strives to obtain the individual active principles in as highly purified a state as possible, in order to simplify the study of the physiological properties of each working by itself, the clinician—when he comes to apply this newer knowledge in the treatment of cases of pituitary hypofunction—will undoubtedly find it necessary to use not one alone but various combinations of these active substances, as will be indicated by the particular types of evidence of hyopfunction which the individual patient presents.

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APPLICATION OF ENDOCRINOLOGY TO GYNECOLOGICAL PROBLEMS

EMIL NOVAK, M.D.
Baltimore, Md.

From the Gynecological Department, Johns Hopkins Medical School.

There are many clinicians whose interest, or lack of interest, in endocrinology is predicated upon their evaluation of the efficacy, or inefficacy, of organotherapy. This is a very narrow and unsound viewpoint.

The relief of human ailments is the natural goal of clinical medicine, but, in so far as the gynecological field is concerned, it may as well be admitted that the accomplishments of organotherapy have been very disappointing indeed. On the other hand, the advances in our knowledge of the physiology of reproduction have been brilliant, and much of this knowledge has been applicable in the interpretation of clinical problems in gynecology. The viewpoint of the gynecologist so fortunate as to be interested in endocrinology will inevitably be broader than that of his more mechanistic colleague, his insight into many problems deeper, and his daily work fuller of satisfaction, interest and zest. Such reasons as this should be incentive enough for the gynecologist to keep in touch with the scientific advances in his particular field of work, regardless of whether or not they are for the present applicable therapeutically.

When we stop to think that pretty much all we know of the physiology of menstruation pertains to its endocrinology, and that the physiology of reproduction has become one of the livest of physiological problems, it is obvious that the gynecologist of today, if he is to practice his specialty intelligently, must of necessity be something of an endocrinologist. If the proper study of mankind is man, the proper study of gynecology is woman, in all her varied biological aspects, rather than merely as a creature possessing pelvic organs of a certain shape, size and position. In many functional gynecological disorders the implications of endocrinology are very obvious, in others less clearly evident, but each year adds new evidence that pathologic physiology as well as mere anatomic changes must be reckoned with in the expla-

nation of gynecologic disease. To illustrate by only the most recent example, we can no longer think of all ovarian tumors as purely parasitic non-functioning growths, for some of them, at least, we now know are capable of producing very profound endocrine effects upon the woman's body.

While the clinician has become quite dependent upon the laboratory worker for knowledge which may be applied in the diagnosis and treatment of disease, there is no need for him to play an entirely parasitic rôle in this regard. Many important endocrinological advances have been made by clinicians, and many more can be made in the future, for the truth-seeking mind and the observant eye are not the monopoly of the experimental investigator, nor is there any scarcity of opportunity for research in the clinical field. It would be unfortunate if clinicians, through consciousness of many past indiscretions and excesses in the endocrine field, should develop such an inferiority complex as to inhibit their future usefulness as contributors to science.

Even the scientists are not beyond criticism, for much time, effort and money have undoubtedly been wasted in studies which could not, by the farthest stretch of imagination, be considered to be of the slightest scientific, much less "practical" value. Many a problem which is perhaps illusory or self-evident has thus been profoundly settled by laborious and expensive experimentation, a brand of scientific investigation to which the Germans have applied the derisive designation of "Scheinwissenschaft." I need not reopen the old wounds inflicted by Lord Moynihan in his Toronto address in 1930, when he so severely castigated the modern medical investigator for directing so little of his effort toward problems the solution of which might in any way tend to lessen the ills of the human race. The quest of truth in itself is praiseworthy, but since it is always fragmentary, why can not the medical investigator search especially for the fragments necessary to piece out our very imperfect knowledge of human disease?

This is not the place to review the advances which have been made in gynecological endocrinology within recent years. I have tried to do this elsewhere, with an expression of our indebtedness to our scientific co-workers in the experimental field. My own part in this symposium, I take it, should be to indicate how some of the raw material supplied to us by the laboratories may be ap-

plied in the interpretation and management of some of the more common gynecological disorders.

With the possible exception of pain, the most important group of symptoms presented by gynecological patients are menstrual aberrations of one form or another. To appreciate the significance of these abnormalities, a knowledge of the normal physiology of the cycle is fundamental. While the gynecologist himself may claim the credit for much of our knowledge concerning the menstrual histology of the ovarian and endometrial cycles, he is glad to acknowledge to the laboratory worker his indebtedness for most of what we know with reference to the physiological forces behind these changes, although we have been kept busy trying to follow the frequent shifts of opinion on this subject.

For the present, it is accepted that both folliculin and progestin are important in the human reproductive cycle, whereas in the strictly sex cycles of the lower experimental animals the folliculin alone is the dominant hormone. In the human, folliculin is present throughout the cycle, being formed first by the growing follicle and later by the corpus luteum, and possibly by other as yet unknown structures. Its function is to produce an increasing growth and hyperemia of the uterine mucosa. Progestin, on the other hand, makes its appearance in the cycle only after ovulation, and is concerned in the production of the secretory, pre-nidatory changes seen in the premenstrual epoch. No other source for progestin than the corpus luteum has as yet been discovered.

The evidence seems quite clear that the endocrine function of the ovary is physiologically subservient to that of the anterior hypophysis. There is still much to learn, however, as to this interlocking mechanism, although more and more it appears that the endocrine effects of the two glands are reciprocal, so that, as Moore and others have urged, the secretory activity of the ovary is an automatic and self-regulating one, through the reciprocal effects of excess or deficiency of the ovarian hormones upon the activity of the anterior hypophysis.

Another point which needs clarification is as to the relation of ovulation and menstruation. Certainly this relation is not an essential one, as has been abundantly shown by studies upon monkeys (Corner, Hartman, Allen). But it is the human problem which needs elucidation on this point, and I think it is quite possible that anovulatory menstruation in women may be found to

be much more common than is now believed. If this suspicion is borne out by future studies, we may have an explanation of many cases of sterility in which menstruation is perfectly normal in every way, and in which all the usual studies show no other ostensible cause for the sterility. It is unfortunate that thus far we have had no method of determining whether or not the individual woman is ovulating. The method of bimanual palpation, so successfully employed by Hartman in determining ovulation in the monkey, has so far been of no value in this respect, and for rather obvious reasons, such as the frequent presence of atretic follicles not distinguishable by palpation from mature follicles. To determine this point in women, I have recently been studying particles of uterine mucosa obtained by premenstrual currettage, usually without anaesthesia. If no secretory activity can be demonstrated in the epithelium, it may be assumed that progestin is lacking, that no corpus luteum is present, and that ovulation has not occurred.

As indicating the possibility of quite typical periodic bleeding, not differing from that of menstruation, in the entire absence of ovulation, I may mention the syndrome characterizing the so-called granulosa-cell tumors of the ovary, now being reported with increasing frequency. When they occur in elderly women, as they most often do, it is common to observe an apparent re-establishment of the menstrual function, at least in the sense of a periodic uterine bleeding, and yet ova are not present in these tumors, nor does ovulation occur. The same thing is true in the case of granulosa-cell tumors in very young children, of which several instances have been recorded. Here again menstruation is observed as a symptom, though without ovulation. In both instances the abnormal bleeding, whether precocious or post-climacteric, has been shown to be due to the production of folliculin by the granulosa cells of the tumor.

While both hormones undoubtedly play a part in the cycle of menstruation, the evidence points more and more to the fact that progestin plays no part in menstruation in the narrower sense of a periodic bleeding. The latter phenomenon appears to be entirely explainable by the fluctuations in the folliculin blood content. This view, now based on increasingly convincing evidence, is one which formerly seemed unacceptable to those of us, including myself, whose impressions were based on histological rather than physiological study. The chief paradox lay in the fact that the follicle

reaches its maximum growth about two weeks before the onset of the bleeding.

With the discovery that, in the human at least, folliculin production is continued by the corpus luteum, this obstacle vanished. Again, the onset of bleeding shortly after the excision of the corpus luteum pointed to the latter as the natural inhibitor of the function, whereas now we know that excision of either the maturing follicle or the corpus luteum, both producing folliculin and the former only folliculin, is followed in due time by bleeding. The evidence therefore indicates that menstrual bleeding is a phenomenon produced by folliculin withdrawal. This is further supported by studies made upon castrated animals or amenorrheic women, in which bleeding is produced by folliculin injection, but only after the lapse of a number of days following the cessation of the injections.

In the same way, the intermenstrual bleeding seen in monkeys, as well as in some women, is apparently explainable by drops in the folliculin level occurring prior to the bleeding. If this concept of folliculin withdrawal is borne out by further work, and if it be extended to certain other types of bleeding, our whole former viewpoint of the mechanism involved must be changed. In the very common gynecological disorder spoken of as functional uterine bleeding, for example, it is not enough to speak of hyperfolliculinism as the underlying cause, as has been done in the past. For that matter, certain types of amenorrhea are likewise associated with folliculin excess, if correlated blood and urine studies are to be accepted as a guide. Some other factor, presumably causing an abrupt drop in the folliculin level, must be concerned in the profuse bleeding so often observed.

My own view is that the explanation of the bleeding is to be sought in the reciprocal interaction of the ovary and the anterior hypophyseal lobe. Moore, Hisaw and others have shown that the secretory activity of the latter is inhibited by a sufficient dosage of gonadal hormone, and Moore's concept of sex hormone antagonism is based on this fact. It is logical, therefore, to assume that the excessive production of folliculin brings about such a pituitary inhibition, and that this in turn brings about a lowering of the folliculin production by the ovary. These drops in folliculin would explain the bleeding phases. Blood and urine hormone studies upon such cases during the bleeding and non-bleeding phases should be

of great interest. What little evidence there is as yet available, however, indicates that the hypophyseogonadal relation is an automatic and self-regulating one, like that of a thermostat.

Theoretically, this form of bleeding should be amenable to treatment with folliculin, and this has indeed a measure of experimental support, but in clinical practice this has not proved to be the case, and such an artificial propping up of the folliculin level has its logical limits, not to speak of uncertainties in dosage. The best results thus far obtained in the organotherapy of this disorder have come from the administration of the so-called luteinizing principles of the urine of pregnant women, which appear to be the nearest clinical approach to supplying the progestin lacking in these cases, for the absence of corpora lutea is characteristic. There is, however, much uncertainty as to the mechanism involved in this form of treatment.

The recent observations of Kaufmann and Clauberg have shown the possibility, in the human castrated patient, of producing hyperplasia of the endometrium by giving large dosages of folliculin, and then, in turn, of converting the hyperplastic endometrium into a pregravid one by means of progestin. The latter, if it becomes available for human use, may be looked to as offering the hope of successful treatment of this very frequent disorder, so often a most distressing one, especially in young patients where radiotherapy is so undesirable.

I have said nothing as yet as to the rôle of the anterior pituitary in the causation of functional hemorrhages, although there is general acceptance of the view that it is in the hypophysis that the underlying cause is to be sought. Leaving aside the discussion as to whether the sex principle of the anterior lobe is single or dual, it is the follicle-ripening effect which seems to dominate in these cases, at the expense of the luteinizing factor. As yet, however, we have no means of correcting this dysfunction, or even of substitution therapy, unless we consider in this latter category the principles obtainable from the urine of pregnant women. Here again we collide with a controversy, for there is increasing evidence that these urinary substances are not identical with the pituitary sex hormones, although in most respects their physiological properties are similar.

To pass to the other quantitative disorder of menstruation, amenorrhea, we encounter even more difficulty and confusion

than in the consideration of menstrual excess. And yet we have advanced far from the day when amenorrhea was explained only by a categorical list of such causes as anemia, obesity and constitutional depravity, and even from the day when, with our new found knowledge of hormones, ovarian hypofunction was added to the list. We know enough now to appreciate that the latter term may cover many endocrine sins, that the interplay of the ovarian secretions must be considered, and, even more, that the interdigitations of function between the ovary and the other ductless glands, especially the anterior pituitary lobe, can not be overlooked.

By clinical methods alone in some cases, in other by such auxiliary methods as blood and urine hormone determinations, basal metabolism studies, or X-ray examinations we can arrive at a fairly intelligent idea of the disorder concerned in the individual case, but not always. But, even if an intelligent endocrine diagnosis be made, rational organotherapy is not available in most cases. Those of thyroid origin are most favorable, both on the grounds of substitutional therapy and because the thyroid is believed to exert a stimulating effect upon many body functions. For the latter reason it is often employed even where a primary thyroid factor is not demonstrable.

For the immediate treatment of the menstrual deficiency, especially in cases in which we assume, usually on rather unscientific grounds, that a hypogonadism exists, some form of ovarian therapy is commonly resorted to, most often without success. The general appreciation of the futility of oral treatment with the older forms of tablets, capsules, or powders of ovarian or corpus luteum substances, or of ovarian residue, is chiefly due to the new light thrown on menstrual physiology, rather than to a mere crystallization of clinical experience and opinion.

With reference to the newer folliculin preparations for hypodermic use, for which such high hopes were originally held, disappointment has resulted, and here again our increased knowledge has enabled us to understand why this should be so. Theelin is capable of producing bleeding in at least a minority of amenorrheic women, but, from what has been said in preceding paragraphs, it is easy to understand that it can not reproduce the menstrual cyclical changes in either the uterus or the ovary. It is certainly not a stimulant of ovarian function, and, indeed, it is a depressant,

as Hisaw and others have shown. To use theelin in amenorrhea is to push the pendulum of the run-down menstrual clock for a single idle, incomplete beat, when what we need is something to wind the clock.

The same may be said of theelol, the hydroxyl theelin derivative which has recently been introduced for clinical use and which is said to be active when given orally. With theelin the effective oral dose is many times, variously estimated at from ten to thirty, the dose required for hypodermic use.

Up to very recently, the question of the dosage of ovarian hormones necessary to bring about "menstrual" bleeding has been a matter of speculation, the point of departure being the dose necessary to bring about an oestrous type of bleeding in animals. There was no direct evidence available from studies upon the human female. In the castrated monkey Hisaw, Meyer and Fevold, as well as Smith and Engle, had been able to produce a pregravid endometrium by the use of folliculin followed by progestin. The discontinuance of treatment was followed, in the observations of Smith and Engle, after six days, by what was apparently a typical menstrual bleeding. Clauberg's observation upon a young woman, who had been castrated some years previously, is of interest, inasmuch as he was able to reproduce in her endometrium, by the use of the two ovarian hormones, a picture typical of the pregravid phase.

So far as I know, the only instance in the literature in which in the human female a genuine menstrual cycle has been reproduced from beginning to end, including a typical menstrual bleeding, is in the extremely interesting case reported by Kaufmann. His patient had been castrated at the age of 17 because of bilateral dermoids, and was of course amenorrheic. Five years later, by the injection of huge doses of folliculin, followed, with some overlapping, by correspondingly huge doses of the corpus luteum hormone, a typical menstrual flow was produced, with desquamation of uterine mucosa, which was recovered from the discharge. Microscopic examination of the cast-off tissue, as well as of further tissue removed with the curette, confirmed the genuinely menstrual character of the flow. The point to be stressed is that, in order to produce this cycle, 320,000 mouse units of the follicular substance (progynonbenzoate) and 90 rabbit units of the corpus luteum hormone were necessary. How fatuous this makes

appear our efforts to treat amenorrhea by the injection of a few hundred units of theelin, either alone or in combination with some unsatisfactory substitute for the corpus luteum hormone, still so inaccessible to the clinician!

The huge dosages employed in the clinical experiments of Kaufmann and Clauberg bear out the deduction of Marrian and Parke in a paper published in 1930. These investigators emphasized that the rat unit, as ordinarily employed, refers to the quantity of the hormone necessary to bring about the characteristic oestrous changes in the vagina, but not in the uterus. To produce the latter, and to reproduce the sex behavior phenomena of oestrus, 200 times the above dose is necessary, i.e. 200 units. If the human dosage is calculated on a weight basis, no less than 400,000 units would be needed to bring about the corresponding histological transformation in the uterine mucosa. While weight is not necessarily a criterion of dosage, in this case it would appear that it is, for the calculated dose of Marrian and Parke is not very far out of line with the doses actually found necessary by Kaufmann and Clauberg.

Kaufmann properly criticizes the tendency to use as a gauge for dosage the amount of hormone eliminated in the urine, which should not be looked upon as necessarily indicating excretion because of an excessive amount in the blood stream. His contention that this hormone, before excretion, may have already played an important biological rôle, appears to be rational. Furthermore, the recent recognition of several forms of folliculin (alpha, beta, theelol), each with a different grade of activity, helps to confuse the picture. But the chief moral to be drawn from this work would seem to be that, if we are to use substitutional ovarian therapy at all, we must work with far larger doses than has been the custom. Furthermore, even with such large doses, there is still no evidence that we can expect a re-institution of the function, for the therapy applies to the individual cycle alone, and would have to be repeated each month.

The dominating rôle of the anterior lobe over ovarian function would suggest that the key to wind the menstrual clock must be sought in the anterior hypophysis. Sometimes, however, the latter itself appears to be run down, and so where shall we seek? Moreover, pituitary therapy is still largely a blank, for the oral preparations now available are apparently worthless from both a

clinical and experimental standpoint, and the hypodermic preparations of pituitary sex hormones, if such they really be, which are obtained from the urine of pregnant women appear to have little or no effect in the stimulation of ovarian function in the human. All sorts of combinations have been suggested, such as the administration of growth hormone with these urinary principles (Evans, Meyer and Simpson), but no one is satisfied with results, and we are still floundering. It is to be hoped that some inspired scientist will soon see our signals of distress, and come to our rescue. In the meantime, it is consoling to know that amenorrhea is a symptom which is rarely of any serious import to the patient, that in itself it causes no harm, and that proper explanation of this fact and reassurance of the patient is often the only treatment needed.

The last in the triad of most important menstrual disorders is dysmenorrhea, more particularly the so-called primary type. It is exceedingly common, and many factors may be concerned in its causation. There is considerable evidence that the immediate factor in the production of the pain may be a heightened irritability of the uterine musculature, and that this may be due to a relative excess of folliculin and a deficiency of progestin. The former appears to be the natural stimulant of uterine rhythmic contractility, the latter an inhibitor. This subject has been fully discussed in a very recent paper by Reynolds and myself, so that I shall not elaborate on it here.

With reference to the organotherapy of the severe symptoms sometimes noted at the menopause, either natural or artificial, little need be said, for I can add nothing that is new. The importance of general regulatory measures and of simple sedatives is accepted by all, but there is much difference of opinion as to the possibilities of organotherapy. The most popular form of the latter, for the present at least, appears to be the administration of theelin, most often hypodermically. Whether or not the favorable results often reported by the patient are to be explained on a purely psychic basis I confess I do not know. Since theelin is undoubtedly deficient in some phases of the menopause, there is at least a semblance of scientific support for its use at this epoch.

The clinician is often hard put to it in his efforts to relieve the very distressing symptoms seen in a small proportion of menopausal patients, and, if the simpler general measures do not avail, I for one shall continue this form of ovarian therapy, at least

until further studies give us a more efficient plan of management. In this connection, it seems both curious and unfortunate that so little effort has been made to discover the mechanism involved in the production of the hot flushes and the other vaso-motor phenomena so characteristic of the menopause, in spite of the fact that the problem presents very obvious difficulties.

Perhaps the outstanding recent contribution of endocrinology to clinical practice has been in the development of the first satisfactory biological test for pregnancy, for the Aschheim-Zondek test, as well as its various modifications, may be looked upon as important by-products of the present-day feverish interest in reproductive endocrinology. As already stated, there is still much discussion as to whether the urinary substances upon which the test is dependent are of pituitary or placental origin, but this question has no bearing on the reliability and value of the test in the diagnosis of normal pregnancy, or its application in the management of such abnormal types as tubal pregnancy, hydatidiform mole, or chorioepithelioma. One advance leads to another, for already it is certain that the remarkable multiple lutein cyst formations in the ovaries of patients suffering with either hydatidiform mole or chorioepithelioma are not true tumors, but that they represent merely an abnormal ovarian response to the abnormal endocrine stimulus emanating from the anterior hypophysis in such cases.

Numerous other examples of the applications of endocrinology in the field of gynecology might be adduced. I have already mentioned that these extend even to the field of ovarian tumors, and I have discussed this general subject in two forthcoming papers. The skeptics of former days are the converts of today, and some of our wisest pathologists appear to be impressed with the potentialities of endocrine studies in relation to tumors, not excluding cancer itself. It will be seen from what has been said that in the field of gynecology, organotherapy has thus far yielded very unsatisfying results, but the therapeutic reward for all the splendid scientific work which has been done is sure to come sooner or later. Why wait for this day to develop an interest in endocrinology, which even in its still undeveloped state can freshen our viewpoint concerning so many clinical problems which had been giving every indication of growing stale?

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CONGRESS DISCUSSION

(Discussion of Papers by Drs. Evans, Collip and Novak)

DR. CARL G. HARTMAN*
Baltimore, Md.

It is a pleasure for me to follow the speakers of this afternoon in point of time, as I have followed them in my thinking in the past.

The clinician occupies two strategic positions as an endocrinologist. In the first place he studies the symptoms of disease and relates certain syndromes to lesions in certain glands. These offer the "lead" to the physiologist and the chemist who work out the details, after which the clinician again functions importantly by utilizing the intermediary findings therapeutically. Laboratory men, I find rather generally, are very glad, despite their protestations to the contrary, to have their discoveries applied to human welfare or to cultural advancement. What the scientific man objects to is the premature heralding of the applications before they have proved themselves.

Following the lead of the pathologist the experimental endocrinologist seeks, by ablation of the gland in question, or injury to it, to repeat the symptoms of the disease; that is, to repeat under controlled conditions, the experiment which nature has already done. If successful, these symptoms are corrected by implantation of the gland substance. Finally the chemist makes extracts and with these seeks to replace the gland substance itself. At first the chemistry is crude and for a long time remains in the "soup" stage, until such men as Evans, Abel, Collip, Doisy, Allen, Hisaw, Swingle and Pfiffner, etc., give us purer products and finally the active principle together with its complete chemical constitution.

I agree, however, with Dr. Novak, in wishing that the clinician did not wait with his human experiments until the last word has been said on any given hormone. The chief reason is that the last word will never be said. Even after the crystalline hormones are placed before us there will be a question if these highly purified substances are really the functional substances in the body. If I trust my ears when I take these to our physiological meetings the

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* Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.

physiology of adrenalin is still under dispute, yet we know enough of its physiological effects to always use it in certain cases clinically.

I should like to mention several points in which the use of the female sex hormones seem to me to have a proved effect, and a few points where information is lacking and alleged effects are not brought out in experiments on monkeys:

1. I am told by conservative clinicians, and we have also just heard several of them say that prolan (follutein Squibb, or antuitrin S. Parke-Davis Co.) will stop functional bleeding. How does it do this? Novak has given up the luteinizing theory. Perhaps the explanation of Dr. G. Van S. Smith appeals to you. At the March meeting of the Boston Obstetrical Society he reported forty-five cases in which, with few exceptions, prolan was recoverable from the urine, during the bleeding. Injection of prolan stopped not only the bleeding, but also the output of prolan. It appears from this that prolan inhibits the secretion of a bleeding factor of the anterior hypophysis.

2. Oestrin certainly builds up the vaginal mucosa of young girls. Dr. Robert Lewis has demonstrated this fact.

3. There is no doubt that oestrin, in the form of amniotin Squibb or theelin, has a very certain effect in the causation of menstruation. It is easy to cause bleeding in the castrate, though larger dosages are required to overcome the inhibitory conditions resulting spontaneously in amenorrhea, as for example, in subnormal females or lactating mothers. However, with reasonable doses, there is scarcely any effect on the uterus other than the bleeding, often not the slightest increase in size or consistency detectable by rectal palpation. Massive doses, of course, do cause growth of the endometrium or the myometrium as we know from ample monkey and from some human experiments. But the threshold for bleeding and for vaginal hypertrophy is so much lower than for growth of the uterus that this fact must be taken into account in evaluating the good that is expected to come to the patients.

4. Now I have made some experiments on the monkey that indicate that such treatments are actually harmful. Theoretically, one would expect this because of the well demonstrated effect of sex hormone injections on the anterior hypophysis. Thus if I select an animal that is menstruating regularly, but not ovulating, and during a given cycle I inject either prolan (follutein Squibb) or

oestrin (amniotin Squibb) that particular cycle remains unaffected. The mechanism of menstruation runs its course as if nothing had been done, but the following cycle is unduly lengthened.

5. Aside from the hemostatic action of the prolan mentioned in (1) I have been unable to find any virtue in the use of it in the monkey. In the rat and the opossum the effect is certain and predictable. Thus in the opossum I succeeded with ten days injection of follutein to bring about a hundred-fold increase in size of the anoestrous ovary. On one occasion one ovary thus produced 212 corpora lutea. Five thousand rat units of the same follutein injected into a monkey may be without effect or a little bleeding may take place during the injections.

Now I have a considerable number of monkey females that persistently menstruate without ovulating, and since it is my desire to secure young embryos, you see I am confronted with a medical situation. I have discovered no magic touch that will bring about ovulation and therefore the possibility of conception. Prolan is almost without effect; hypophyseal implants or potent extracts cause growth of the follicles, but this growth goes wild, the follicles are injured or prematurely luteinized and ovulation fails to materialize. Under these conditions the effect on the uteri is also minimal and not at all fitted to receive and imbed the egg.

In no case therefore, is the female stimulated to continue its cycles. There is as yet no key to wind up the clock and keep it going. If the clock happens to be of the five and ten cent variety there seems little need to expect one that will run and keep time. A little guilding might help psychically, however; but that is out of my field.

DR. ROBERT T. FRANK
New York

Mr. President, after listening to this admirable symposium on the female sex hormones, I feel somewhat stunned at the complexity that the subject has assumed. I hope that in the future some simplification will develop. I am afraid to discuss the dynamics of the anterior hypophysis, and I will speak of the prolans (anterior pituitary *like* substances found in the urine) and of the female sex hormone, because this element occurs not only in the

female, but in the blood and urine of the male. Neither will I enter into the biological discussion raised by the two first speakers.

I will say here that the pregnancy reaction can continue after the death of the fetus. We had a case of a woman who delivered herself of a full-term child. The placenta stayed in the uterus for 17 days without causing hemorrhage, and during that time the pregnancy test continued strongly positive. We have a test to determine whether the fetus is alive or not. The female sex hormone test becomes inactive within twenty four hours after the death of the fetus. I am sorry Dr. Collip did not go more fully into this test.

I think that the ether insoluble estrogenic factor obtained from placenta, given by mouth, promises results, if theelin therapy ever becomes practicable. It would require three or four hundred thousand units in the human and then it requires 90 units of progestin in addition to bring the uterus to menstruation in the castrate. But if you succeed in this, once, what have you done then? It is an isolated and useless effect. I started working with these extracts in 1914. At that time two kilograms would have been required to produce an effect. Now we have the highly potent concentrated extracts, but clinically we are no further on.

I will show three slides to demonstrate how clinical investigation may throw light on the sex hormone studies. Here is an individual who falls into the class of basophilic adenoma. She is obese, plethoric, hirsute, pig-eyed, with depressed basal metabolism and high blood pressure. We made a fairly thorough hormone study in this case. (See Chart.) Clinically this shows that pituitary basophilia stimulates the ovaries, increases the output of female sex hormone and produces amenorrhea by excessive and prolonged uterine stimulation. In the case of basophilic adenoma the urinary output of the female sex hormone is greater than in the normal pregnant female.

Our studies show that it is only by collaboration of the laboratory worker and the clinician that we can hope to clarify this subject. We hope that the laboratory men will at last give us usable preparations. Critical clinicians feel entirely disillusioned about the preparations so far available.

DR. HENRY ALSOP RILEY
New York City

I have appreciated very much the opportunity of hearing these most interesting expositions of the scientific aspect of the investigation of the hormones of the hypophysis and gonad as given this afternoon by Drs. Collip and Evans.

I would like to present a preliminary report on the application of these scientific discoveries to the clinical problem of migraine. This work has been carried on by Dr. Richard M. Brickner, Dr. Raphael Kurzrok and myself at the College of Physicians and Surgeons and the Neurological Institute, supported by the financial aid of the Josiah Macy, Jr., and the Chemical Foundations. I have some hesitancy in presenting the material on account of the small group of patients so far investigated but I am doing so with the hope that similar investigation may be made at other centers.

The connection between the functional activity of certain endocrine glands and the migrainous seizure has been emphasized for many years as one of the phases of our investigation of migraine, it seemed most important to study the excretion of the sex hormones in the urine of patients suffering from migrainous attacks. The relationship of the ovary has, of course been emphasized for centuries principally because of the relation between the migrainous seizure and menstruation and the fact that migraine is usually limited to the menstrual life in females, failing to appear during cessation of ovarian functions such as that occasioned by pregnancy, lactation and the spontaneous or operative menopause. The hypophysis has been implicated principally on account of its position in relation with many of the structures whose involvement would explain so many of the symptoms of migraine. The relation of the hypophysis to the migrainous seizure has also been emphasized on clinical grounds. The hormones which we have investigated are prolan secreted by the hypophysis and theelin produced by the ovary. There were thirteen patients in all; two males and eleven females, three of whom were past the menopause, either spontaneously or artificially. They were all sufferers from simple migraine. A preliminary group of patients was studied by means of only single unrepeated specimens but the group reported here was investigated for the presence of hormones over a period of about three weeks during which time all of the patients had one or more head-

aches and all of those who were menstruating passed through one of their periods. As a result of the study of the excretion of the hormones and the apparently related occurrence of the migrainous attacks we came to the following conclusions:

1. While theelin was almost consistently absent from the patients forming the preliminary group in whom only single specimens were examined, the study of the daily urine excretion recorded the occasional presence of the hormone in all but one of the menstruating individuals and in this woman the menopause was imminent. In one woman who had passed a natural menopause, theelin was absent, as was the case also in another woman in whom the menopause had been induced by operation. In all of those in whom theelin was demonstrated the hormone was absent sporadically and when present the amount of theelin rarely exceeded five rat units per liter. Only exceptionally did the quantity of hormone reach the ten to twenty rat units which is considered the normal amount for women within the menstrual age.

2. No demonstrable relationship could be determined between variations in the excretion of theelin and the occurrence of headache.

3. In all of the cases, prolan was excreted. In the two women past the menopause and the one approaching it prolan was present almost daily in large quantities; in the remaining 11 cases the hormone was demonstrated intermittently and in varying amounts.

4. In the entire group of patients investigated, twenty-nine individual headaches occurred. Headaches which continued over consecutive days were considered, for purposes of tabulation, as constituting a single attack. In two patients the headaches were so continuous as to constitute a status migrainicus, not being separable into single headaches, and therefore could not be included in the number (29) given above.

In 20 out of the 29 instances the headache was preceded or accompanied by the appearance of prolan in the urine. In calculating the number of days by which the appearance of prolan antedated the headache the interval was determined by counting from the first day of the appearance of the hormone to the beginning of the headache. In one patient in whom the initial appearance of prolan antedated the headache by an interval of three days—prolan appeared on each of the three consecutive days and disappeared

with the occurrence of the headache. In one patient on one occasion prolan was demonstrated four days before the headache, but continued to appear in the urine for three of the four days. In another instance, in which the headache was preceded by an interval of six days, the prolan continued to occur on each of the six days, failing to appear only on the day of the headache. In four instances the continuous excretion of prolan extended through at least a part of the period of the headache. In one patient the prolan appeared for two days, was absent for one day and recurred coincidentally with the occurrence of the headache. The incidence of headache and prolan excretion limited to a single day coincided in only two instances. The interval by which the one antedated the other was, in 7 instances, one day; in 4 two days, in 5 three days, in 1 four days, and in 1 six days.

In the two patients presenting a status migrainicus, the excretion of prolan was practically uninterrupted. There was, therefore, a continuous relationship between the appearance of prolan and the occurrence of headache. In one patient, a practically continuous prolan excretion occurred over the period of observation, but during this time only three headaches took place. In this patient it was therefore impossible to relate the headaches to any particular day of prolan excretion.

5. In nine of the twenty-nine headaches, no prolan-headache relationship was demonstrated. In seven of the nine headaches, however, the determination of an exact relationship between the appearance of prolan and the occurrence of headache was rendered impossible by the absence of urine specimens in the graphs. In the remaining two of the nine, the requisite number of specimens was obtained but the headache occurred without the antecedent appearance of prolan.

6. Occasionally, prolan appeared without the subsequent development of headache. Of the three cases showing almost daily prolan excretion, one individual failed to develop a headache on only one day, another was free from headache on only an occasional day, but the third, as stated above, was free from headache the major part of the time of observation. In the remaining 8 patients, in whom prolan appeared intermittently, a headache failed to follow the excretion of the hormone only five times.

7. Of the eight menstruating women, seven had attacks with menstruation. No definite difference could be determined in the

relationship between menstruation, headache, and the excretion of prolan, from the headache—prolan relationship occurring at other times.

8. Prolan was excreted in association with all menstrual periods except in the one case in which the requisite specimens were not obtained.

9. Nine female patients were injected with 2 cc. of follutein and seven developed an attack of migraine within four to twelve hours. The attack was either mild or severe but always presented the migrainous characteristics which were typical for the individual.

10. Only two men were studied during the period covered by this preliminaty investigation. One man had six, and the other had nine headaches. In the patient with six attacks, specimens preceding one headache were lost, but all of the other attacks were associated with the excretion of prolan within a period not exceeding three days. In the other male patient with nine headaches, specimens were lost preceding one attack. Of the remaining eight attacks, headache was associated with the excretion of prolan in only four instances; he, therefore, had four headaches without the associated excretion of prolan.

Follutein was administered to one patient twice, the injections being separated by an interval of six days. A typical two day headache developed following the injection after three days. After the second injection no headache developed.

The experiments have not yet been controlled by the study of a non-migrainous group over a comparable length of time. This will be one of the next steps in our investigation. I believe that this is the first tangible evidence presented that the migrainous seizure can be definitely related to some perhaps perverted activity of the gonad or the hypophysis. We do not believe that this solves the problem of migraine by any means but we do believe that it presents a very useful point of departure for further investigation and for the treatment of the disorder. Without doubt further reports of this investigation will follow.

On account of the close clinical and theoretical relationship between migraine and the other more strictly motor manifestations of the convulsive state, the so-called epilepsies, we are applying this hormonal study to the occurrence of convulsions also. We are not in any position yet to report anything in regard to this

study but when sufficient material is accumulated we expect to do so.

I appreciate very much the opportunity for presenting this material before the Congress and I wish to thank Dr. Harvey Cushing and Dr. John King for their courtesy in placing me on the program.

PRESENTATION OF KEYES MEDAL

EDWARD LAWRENCE KEYES

1843–1924

For each of us today as in Plato's time there is a higher as well as a lower education. . . . This higher education so much needed today is not given in the school, is not to be bought in the market place, but it has to be wrought out in each one of us for himself; it is the silent influence of character on character, and in no way more potently than in the contemplation of the lives of the great and good of the past, in no way more than in "the touch divine of noble natures gone."

WILLIAM OSLER
1901 "*Books and Men.*"

DR. WILLIAM C. QUINBY

Representing the American Association of Genito-Urinary Surgeons

We meet today to commemorate the life and work of Edward L. Keyes, a surgeon of New York City, whose energy and foresight founded in 1886 the American Association of Genito-Urinary Surgeons, and who was its first president.

Born in 1843, he received his academic training at Yale from which he was graduated in 1863, leaving college to join the army as a captain on the staff of his father, Major General Erasmus Darwin Keyes. After a year's service during these closing months of the war Keyes entered the New York University Medical College from which he was graduated in 1866 after the customary two years' training, with the degree of Doctor of Medicine. One of his grandfathers had been a physician—often a potent factor in determining a youngster in the choice of his career—and besides there was still ever present the war with its sorrows, its bitterness, its wastage of human life of which he had doubtless already seen aplenty. Young men were serious in those times and none more so than Keyes, who had thus decided to devote his life to bettering the lot of his fellowman.

As a medical student Keyes must have been outstanding, for during this time he won the favorable notice of his preceptor Dr. Wm. H. Van Buren, the Professor of Surgery and one of the most able and popular surgeons of the city. By Van Buren's advice

Keyes Medal Presented to
Dr. A. N. Richards

after graduation Keyes went to Paris, and it is easy to see in all his subsequent career the impress of this year spent in that scientific medical atmosphere.

Here Pasteur was actively at work and only a couple of years earlier had solved the disease of the silk worm. Claude Bernard was already famous and in this same year of '67 Lister introduced antiseptic surgery in the famous paper published in the Lancet. Also in this year was held in Paris the first international medical congress. The Hôtel Dieu and the Salpétrière were replete as ever with pathology. Thus the industrious student could hardly fail to meet with daily examples long to be remembered for the profit of future patients of his own.

Returning to New York Keyes immediately took a prominent position among his medical colleagues. By the advice of Van Buren he had devoted much of his attention to the study of dermatology while in Paris, so that naturally he sought at an early date to advance the knowledge of medicine in this field.

In November '69 there appears a review by Keyes on dermatology in which after abstracting some two dozen articles from the foreign literature, the remark is made "America has only recently waked up to the fact that dermatology is worthy of special investigation."

Such communications reveal today merely the earnestness of a youngster intent on winning his spurs. His clearness of thought and rigid resolve to avoid all self-deception come clearly forth in his next communication to the Pathological Society in '71 in which he relates his experience in the case of a woman suffering from an aneurysm of the mesenteric artery. It was decided to treat this by "galvano-puncture" a modality but imperfectly understood in those days. Accordingly Keyes undertook a series of experiments on dogs under ether, needling the aorta. Needles of many different compositions were tried and the conclusion reached that gold needles produced the best clot.

The patient was operated on four times—one needle being used at the first operation, two at the second, six at the third, and eleven at the fourth. The first operation lasted ten minutes. The last one an hour and five minutes. After each operation the walls of the sac became firmer, and the patient had a better appetite and less pain. Finally only one bruit could be heard over the tumor.

But the patient gradually failed and died, and at autopsy three aneurysms were found. One of the innominate artery at its origin from the aorta, filled with firmly organized clot; the second of the aorta opposite the 6th and 7th vertebrae. Part of the contents of this was also clotted. Neither of these had been detected during life. In the abdomen lay the sac which had been treated. There was no peritonitis but the contents of this aneurysm lacked concentric striation to indicate any special action of the needles. Keyes then makes the note that it was fortunate that the other aneurysms existed; otherwise what coagulation had occurred in the one under treatment would have been set down to galvanism. In fairness to the method, however, he called attention to the fact that the needling had done no harm and should be further investigated.

Here at the age of twenty-eight we have evidence of an honesty, industry and clarity of vision which must surely make their possessor a marked man.

And then, in 1874 appeared the immediately famous text book "Surgical Diseases of the Genito-Urinary Organs, including Syphilis" written in collaboration with his preceptor Van Buren and later to run through many editions.

Such outstanding industry was rewarded by Keyes' appointment as Professor of Dermatology; adjunct Professor of Surgery and Visting Surgeon to Bellevue Hospital (Medical College) and here he gave the first course of lectures in dermatology in the United States.

Soon, on the heels of all this we find Keyes making a brilliant report in 1876 at the International Congress of Medicine in Philadelphia on "the effect of small doses of mercury in modifying the number of the red blood corpuscles in syphilis." In this article, based on accurate blood counts with the aid of an instrument imported from Paris, it was clearly shown that mercury is a tonic when properly given. Salivation was no longer necessary in order to control syphilis. The accuracy of the results here reported was immediately accepted and this form of treatment generally adopted.

But the art of medicine rather than its scientific side was of greater attraction to a man of Keyes' sympathetic nature, and though his graciousness and clarity of diction might make him the choice of the Academy of Medicine when it was dedicating a new home, it was in the solution of the manifold problems of the

consulting room that he most truly shone. Here his earnest sympathy and unswerving morality often turned despair into hope, defeat into victory, for the patient.

This nobility of character combined with great professional skill is best brought out by an incident related by his son. "In his youth he had been isolated a month with Charles O'Connor when the latter returned from Europe with smallpox, and years after when the man who had smashed the Tweed Ring was dying at Nantucket and was told that the family had sent for Keyes, he said, 'Don't let him come; this time I want to die.' "

Alfred Newton Richards: It has been said that there are three sure signs characteristic of a genuine student: an absorbing desire to know the truth, an unswerving steadfastness in its pursuit, and an open, honest heart, free from suspicion, guile and jealousy.

These attributes you possess in full measure. Your ingenuity has overcome obstacles, let light into dark places, and made clear many uncertainties of bodily function. You are a worthy successor of your predecessors Heidenhain, Ludwig and Bowman.

Fruitful in the past, your work is also of high hope for the future.

Sir: In honoring you by the presentation of this medal commemoratory of Keyes, its founder, the American Association of Genito-Urinary Surgeons at the same time honors itself.

REPLY BY DR. A. N. RICHARDS

Mr. President, Dr. Quinby, Members of the Congress: I am extremely proud to be the first recipient of the medal which bears the name of this great gentleman and to be permitted to carry this magnificent trophy to the University which supports me.

In accepting it, I do so as the representative of a group of my collaborators to whom the greater share of the credit for our work is due. I accept it with no illusion that what has been learned in our laboratory is more than a very small part of what we now know and a very minute fraction of what we must know before we can have deep understanding of the function of the kidney. I accept it in the hope, and with some confidence in the hope, that we now possess new methods with which it may be possible to reinforce or correct with demonstrable facts some of our current hypotheses concerning the functions of the renal tubule. And finally I accept

it with recognition of its implicit obligation to work with as much industry and speed as is consistent with sound observation in order to place in the hands of the clinician information of true usefulness in his indispensable service to man.

I beg of Dr. Quinby to convey my humble and profoundly appreciative thanks to the Association which he represents and to which I am so deeply indebted.

DR. HARVEY CUSHING

We shall look forward to the forthcoming Congress as the years roll round. I want to express my regret that the Physicians see fit to leave this Congress. I feel that this Congress has an important rôle to play in national affairs, and I hope that later on the Association of American Physicians will realize this and be willing to rejoin the Congress. I feel that our work will go on. I want to thank the gentlemen from New York and Baltimore who have given us these magnificent papers. In regard to this work, even if we cannot hope to seize something for immediate application, we should not be discouraged. Laboratory men have gone ahead and as yet we don't understand their language. As the work progresses, important practical things will come out of it as regards clinical application.

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